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# Critical Care [ALERT]

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

SPECIAL FEATURE

## Palliative Care in the ICU: Benefits and Controversies

*By Leslie A. Hoffman, RN, PhD*
*Professor Emeritus, Nursing and Clinical & Translational Science, University of Pittsburgh*

The quality of care provided to patients and their families at end-of-life has become a key element in discussions on U.S. health care system reform. Palliative care focuses on symptom management, communication about the goals of care, matching the care delivered with patient values and preferences, and support for the family.[1] The Institute of Medicine and societies representing critical care clinicians support palliative care as a priority area for ICU quality improvement.[1-4] However, guidance on how this can best be accomplished remains limited. The purpose of this article is to review support for the introduction of palliative care, models for structuring a clinical initiative to enhance palliative care, and literature supporting the success and challenges of attempts to accomplish this goal.

### SUPPORTING EVIDENCE

Despite widespread enthusiasm, evidence supporting positive outcomes from unit-wide initiatives to implement palliative care or increase use of components of this care is sparse.[5] Trials using a randomized design are difficult to implement and quality-of-life outcomes can be difficult to measure. There is, however, compelling evidence of the success of this approach from studies conducted in the outpatient setting. In a study of 151 patients with metastatic non-small lung cancer, those randomized to early palliative care reported a better quality of life and fewer depressive symptoms.[6] Fewer patients in the early palliative care group received aggressive end-of-life care (33% vs 54%), but median survival was longer (11.6 vs 8.9 months). A recent editorial[7] shared the experience of a patient with pulmonary fibrosis who, as a consequence of her diagnosis, lived a "bed to chair" existence. Her past history included 21 hospital admissions within 2 years for varied symptoms. Referral to palliative care

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resulted in a prescription for low-dose opioids to help with her dyspnea, low-dose benzodiazepines to help with her anxiety, and scheduled home care visits. Hospitalizations and frequent phone calls to her pulmonologist stopped and she started going out with friends because she felt better. Regular visits by home care nurses, not tied to her symptoms, provided support and she died 2.5 years later due to a ruptured aortic aneurysm.

## MODELS FOR INITIATING PALLIATIVE CARE

Two models have been described for integrating palliative care into critical care practice — the "consultative" model, which focuses on use of an institutional-based consult service, and the "integrative model," which focuses on interventions directed by the critical care team.[5] When using the consultative model, palliative care is provided on a consultation basis for patients viewed at highest risk of death or at high risk for poor functional or cognitive outcomes at ICU discharge. Those who provide palliative care vary but consultation most commonly involves assessment by an advanced practice nurse or interdisciplinary team that includes members with diverse experience, e.g., physician, nurse, social worker psychologist, and/or chaplain. Some ICUs use "triggering criteria" that lead to initiation of a palliative care consultation.[5] When the integrative model is used, palliative care is imbedded in the daily management of all patients in the ICU and initiated by the critical care team when deemed necessary. To promote ability to provide this care, clinicians have access to several online programs for advanced training. Examples include the End of Life Nursing Education Consortium (EL-NEC) Critical Care training program,[8] Initiative for Pediatric Palliative Care program,[9] and Critical Care Communication Skills program (C-3) for critical care fellows.[10] A National Institutes of Health initiative, the IPAL-ICU Project, is designed to provide a comprehensive online repository of resources for providing palliative care in the ICU.[10]

## EVALUATION OF SUCCESS

Several studies have evaluated outcomes of initiatives designed to integrate palliative care into the critical care setting, with varying success. Curtis and colleagues reported no improvement of family-assessed quality of dying or family satisfaction with care following introduction of an intervention that consisted of clinician education, local champions, academic detailing, feedback to clinicians, and system support.[11] However, nurse-assessed quality of dying improved significantly and ICU length of stay decreased. The study enrolled 253 patients/families in the pre-phase and 337 patients/families in the intervention phase.

Penrod and colleagues conducted a prospective multisite study that evaluated how extensively clinicians employed a care and communication bundle designed to promote palliative care in two academic ICUs and one community hospital ICU.[1] This study enrolled 518 patients and 336 family members. Initiation of bundle measures varied substantially. Highest ratings were achieved for pain assessment and management (80%) and lowest for distribution of an informational brochure (8%) regarding palliative care. Less than 20% of families participated in interdisciplinary family meetings by ICU day 5, as advocated in the bundle.[1]

White and colleagues conducted a single-center trial testing outcomes of a nurse-led intervention designed to improve integration of palliative care in the ICU.[12] The intervention, titled Four Supports, involved adding a nurse to the critical care team to facilitate integration of palliative care. In this small trial, outcomes were highly successful. The nurse, who was titled a family support specialist, met an average of 48 ± 36 minutes per day with clinicians and patient/families. The intervention was positively rated by > 90% of physicians and families in regard to improving timeliness of communication, facilitating discussion of patient values and preferences, and improving care.[12]

## PALLIATIVE CARE IN DAILY PRACTICE

As indicated by these findings, the goal of integrating palliative care into critical care practice is not easily accomplished. New tools can make this goal easier to achieve.[8-10] Willingness to designate a unit-based care provider can improve integration, with highly positive ratings from physicians, nurses, and patients/families.[12] However, unfortunately, studies continue to suggest that clinicians are not fully addressing patient values and preferences as part of daily care. In a study of cystic fibrosis physicians, those surveyed described numerous barriers to communicating with patients, including concern for taking away hope and uncertainty about when to initiative such discussions.[13] From a survey of 278 elderly patients (80 ± 9 years), Heyland and colleagues reported that before hospitalization, most patients (76%) had thought about end-of-life care and only 11.9% preferred life-prolonging care.[14] Most (73%) had formally named a surrogate decision maker. Of patients who discussed their wishes, only 30% had done so with the family physician and 55% with a health care team member. Agreement between patient preferences and medical record documentation was 30%.

As with most problems, the solution may lie in the middle. In a recent editorial, Quill and Abernethy advocated merging the two proposed models (consultative and integrative) for providing palliative care.[15] To expand palliative care delivery, they propose a model that distinguishes primary palliative care (skills that all clinicians should have) from specialist palliative care (skills for managing more complex and difficult cases), so that they can coexist and support each other. Representative skills that might be required in each situation are listed in the table.

The model proposed above addresses three concerns. First, it is unclear whether there is sufficient availability of those specializing in the provision of palliative care to meet current and future needs. Second, many of the components of palliative care are within the current skill set of the critical care team and therefore can be easily included in the plan of care on a daily basis. Third, there is a concern that delegation of palliative care to a group of "specialists" risks further fragmenting care by diverting concern for symptom management and psychosocial support to others. As with changes in other aspects of care practices, understanding of how to best accomplish goals in a highly complex environment is evolving and strategies for ensuring integration of palliative care are becoming more clearly defined. ■

### REFERENCES


1. Penrod JD, et al. Meeting standards of high-quality intensive care unit palliative care: Clinical performance and predictors. *Crit Care Med* 2012;40:1105-1112.

2. Lanken PN, et al. An official American Thoracic Society clinical policy statement: Palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008;177: 912-927.

3. Davidson JE, et al. American College of Critical Care Medicine Task Force 2004-2005. Clinical practice guidelines for support of the family in the patient-centered intensive care unit. *Crit Care Med* 2007;35:605-622.

4. Selecky PA, et al. Palliative and end-of-life care for patients with cardiopulmonary diseases: American College of Chest Physicians position statement. *Chest* 2005;128:3599-3610.

5. Nelson JE, et al. Models for structuring a clinical initiative to enhance palliative care in the intensive care unit: A report from the IPAL-ICU Project (Improving Palliative Care in the ICU). *Crit Care Med* 2010;38:1765-1772.

6. Temel JS, et al. Early palliative care for patients with metastatic non-small cell lung cancer. *N Engl J Med* 2010;363:733-742.

7. von Guten CF. Palliative care for pulmonary patients. *Am J Respir Crit Care Med* 2010;182:725-726.

8. End of life nursing education consortium (ELNEC) – Critical care train the trainer program. Available at: http://www.aacn.nche.edu/ELNEC/CriticalCare.htm.


**Table. Examples of Skills Included in Primary and Specialty Palliative Care**

| Type of Palliative Care | Examples of Component Skills and Activities |
|---|---|
| Primary Palliative Care | • Management of pain and symptoms<br>• Management of depression and anxiety<br>• Discussion about prognosis, treatment goals, symptom management, code status |
| Specialty Palliative Care | • Management of refractory pain or other unrelieved symptoms<br>• Management of complex depression, anxiety, and distress<br>• Assistance with conflict resolution regarding goals or methods of treatment by surrogates or the critical care team<br>• Assistance in addressing postdischarge concerns |

*Adapted from Quill and Abernethy[15]

9. Initiative for pediatric palliative care curriculum Available at: http://www.ippcweb.org/curriculum.asp.

10. Center to advance palliative care. Available at: http://www.capc.org.

11. Curtis JR, et al. Integrating palliative and critical care: Evaluation of a quality-improvement intervention. *Am J Respir Crit Care Med* 2008;178:269-275.

12. White DB, et al. Nurse-led intervention to improve surrogate decision making for patients with advanced critical illness. *Am J Crit Care* 2012;21:396-409.

13. Dellon EP, et al. Physician practices for communicating with patients with cystic fibrosis about the use of noninvasive and invasive mechanical ventilation. *Chest* 2012;141:1010-1017.

14. Heyland DK, et al; for the ACCEPT (Advance Care Planning Evaluation in Elderly Patients) Study Team and the Canadian Researchers at the End of Life Network (CARENET). Failure to engage hospitalized elderly patients and their families in advance care planning. *JAMA Intern Med* 2013; Apr 1. [Epub ahead of print.]

15. Quill TE, Abernethy AP. Generalist plus specialist palliative care: Creating a more sustainable model. *N Engl J Med* 2013;368:1173-1175.

## ABSTRACT & COMMENTARY

# Noninvasive Ventilation: Still Underused in Acute Respiratory Failure

*By David J. Pierson, MD, Editor*

**SYNOPSIS:** Nationwide from 2000-2009, there was a steady increase in the use of noninvasive ventilation (NIV) in managing acute respiratory failure, although the percentage of potentially eligible patients who receive it remains small. Importantly, the proportional increase was less for chronic obstructive pulmonary disease ([COPD] in which the evidence is compelling and NIV is the standard of care) than for non-COPD causes of respiratory failure (in which the evidence is weaker or conflicting).

SOURCE: Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: A population-based study. *Ann Am Thorac Soc* 2013;10:10-17.

Using discharge data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project from the Agency for Healthcare Research and Quality (AHRQ) for the years 2000-2009, Walkey and Wiener investigated population-based trends in the use of noninvasive ventilation (NIV) among patients with a diagnosis code for acute respiratory failure (ARF). Their objective was to compare utilization trends and outcomes with NIV use in patients with and without chronic obstructive pulmonary disease (COPD). Of the 78 million discharges from acute care hospitals nationwide during the study interval, the investigators identified 2,380,632 adults (3% of the total) whose hospitalization was coded for ARF. A diagnosis of COPD was present in 900,750 of these (37%). Across the United States, there was a steady increase in the population-based incidence of ARF over the 10-year study period. There was also a steady increase in the use of NIV among patients with ARF: from 8.6 to 39 per 100,000 U.S. residents for COPD, and from 6 to 39 per 100,000 for non-COPD causes. The use of invasive mechanical ventilation increased 7% for COPD patients with ARF compared to a 73% increase for non-COPD causes of ARF.

The proportion of patients with COPD who received NIV increased 250% during the study period, but only from 3.5% in 2000 to 12.3% in 2009. The corresponding percentages for patients with non-COPD ARF were 1.2% and 6.0% (a 400% increase). Thus, from 2000 to 2009, the rate of "uptake" for NIV as a ventilation approach for ARF in U.S. hospitals was greater for non-COPD causes of ARF than for exacerbations of COPD.

The authors also examined outcomes of NIV — specifically NIV failure and the subsequent use of invasive mechanical ventilation — for patients with COPD and cardiogenic pulmonary edema, conditions in which the evidence supporting its use is strongest, as compared with those with pneumonia, sepsis, and other causes for ARF with weaker or conflicting evidence in favor of NIV. NIV was more likely to fail in this latter group. In addition, patients who required invasive ventilation after NIV failure were more likely to die in the hospital than patients who received mechanical ventilation via endotracheal tube from the beginning.

### COMMENTARY

NIV is now well established as the standard of care for ARF complicating COPD, in which setting it reduces mortality, complications, lengths of stay, and costs. For other causes of ARF, the strength of the evidence supporting NIV varies from fairly solid in cardiogenic pulmonary edema to much less strong (or contradictory, or lacking) in most other clinical settings. Thus, the findings in this population-based study covering a period

in which the evidence supporting NIV in COPD was already well known, with practice guidelines recommending its use, are discouraging. The overall use of NIV in ARF did increase across the United States from 2000-2009 — but only to about 1 in 8 patients with COPD — and it increased even more proportionally in circumstances (non-COPD) for which NIV is not generally the standard of care.

Two other recent studies deserve mention. Chandra and colleagues examined data from the AHRQ's Healthcare Cost and Utilization Project's Nationwide Inpatient Sample to study trends in NIV usage in patients admitted because of acute exacerbations of COPD (AECOPD).[1] Among 7.5 million U.S. admissions for AECOPD from 1998-2008, the use of NIV steadily increased. However, as in the Walkey study, the proportions remained discouragingly low: from 1.0% to 4.5% of all patients. Chandra et al did not study ARF per se, but focused on the condition (AECOPD) in which the evidence of benefit from NIV, in the setting of a severe exacerbation, is most compelling. In their study, only in the last year of the 11-year observation period did NIV overtake invasive mechanical ventilation as the most frequently used form of ventilatory support in these patients.

Unlike the clinical trials in which the efficacy of NIV in AECOPD and other settings for ARF has been investigated — with the conditions of interest carefully defined and therapy administered according to study protocols — the Walkey and Chandra studies looked at the real-world use of NIV for ARF across America. Similarly, in the April issue of the *Journal of Hospital Medicine*, Tsai and colleagues report on their study of NIV use among patients with AECOPD who are admitted through the emergency department.[2] They used data from the 2006-2008 Nationwide Emergency Department Sample, a component of the AHRQ's Healthcare Cost and Utilization Project. Of approximately 101,000 visits for AECOPD in each of the study years, 96% resulted in hospital admission. The use of NIV in admitted patients ranged from 14% in 2006 to 16% in 2008 ($P = 0.049$ for the increase). However, among the 4700 hospitals whose data were included in the study, usage of NIV in patients with AECOPD varied enormously — from 100% to 0%, with a median of 11% of patients. NIV use tended to be greater in high-case volume Northeastern hospitals.

By propensity score analysis, NIV use, compared with invasive mechanical ventilation, was associated with lower inpatient mortality (risk ratio, 0.54; 95% confidence interval [CI], 0.50-0.59), shortened hospital length of stay (-3.2 days; 95% CI, -3.4 to -2.9 days), lower hospital charges (-$35,012; 95% CI, -$36,848 to -$33,176), and lower risk of iatrogenic pneumothorax (0.05% vs 0.5%, $P < 0.001$). Thus, while also confirming previous findings of the beneficial effects of NIV in AECOPD, Tsai et al documented the low overall use of this therapy as recently as 2008.

These studies all suffer from their use of administrative databases (that is, discharge coding) rather than clinical data to identify patients with ARF, COPD, and other diagnoses, as well as from not having examined the study questions prospectively. Nonetheless, the message seems clear: As in many other areas of health care, "clinical uptake" — the translation of research findings into bedside day-to-day practice — lags way behind the evidence. In their thoughtful editorial accompanying the Chandra study, Elliott and Nava consider the possible reasons for this in the case of NIV for AECOPD.[3] It is hard to accept "unfamiliarity with the evidence" on the part of intensivists and respiratory therapists, as a reason, since surely in 2013 everyone practicing critical care has to know that NIV improves outcomes in AECOPD. But ingrained practices are hard to change. In the respiratory care field, especially, knowledge translation has been challenging despite strong evidence in a number of areas.[4] Let us hope that future studies using databases from the current decade will show a dramatic increase in the use of NIV in those settings — AECOPD especially — in which it has been shown to save lives and improve other outcomes in the everyday practice of critical care. ■



REFERENCES


1. Chandra D, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med* 2012; 185:152-159.

2. Tsai CL, et al. Comparative effectiveness of noninvasive

ventilation vs invasive mechanical ventilation in chronic obstructive pulmonary disease patients with acute respiratory failure. *J Hosp Med* 2013;8:165-172.

3. Elliott MW, Nava S. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: "Don't think twice, it's alright!". *Am J Respir Crit Care Med* 2012;185:121-123.

4. Pierson DJ. Translating evidence into practice. *Respir Care* 2009; 54:1386-1401.

## ABSTRACT & COMMENTARY

# Are Morbidly Obese Patients Receiving Invasive Mechanical Ventilation at Higher Risk of Death?

***By Betty Tran, MD, MS***

*Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago*

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

SYNOPSIS: **Using a national database, the authors found that morbidly obese patients undergoing invasive mechanical ventilation had a similar risk of in-hospital mortality compared to non-obese individuals, despite having higher rates of invasive mechanical ventilation and tracheostomy.**

SOURCE: Kumar G, et al. Outcomes of morbidly obese patients receiving invasive mechanical ventilation: A nationwide analysis. *Chest* 2013; Jan 24. [Epub ahead of print.]

Given inconsistent results from prior studies that have focused on outcomes in the critically ill, obese population, Kumar and colleagues sought to clarify whether morbidly obese (BMI ≥ 40 kg/m$^2$) adults receiving invasive mechanical ventilation (IMV) had significantly different outcomes compared to their non-obese counterparts. The authors used ICD-9-CM diagnosis and procedures codes from the Nationwide Inpatient Sample (NIS), a publicly available, all-payer database approximating a 20% stratified sample of U.S. community hospitals, to identify 4,070,419 morbidly obese individuals who were hospitalized in the United States between 2004 and 2008. Of these, 119,759 (2.9%) required IMV. Compared to non-obese individuals hospitalized during that time, morbidly obese patients had 1.37 (95% CI, 1.20-1.57) times higher odds of receiving IMV. Morbidly obese patients receiving IMV were also significantly younger, more likely to be female and black, more likely to be admitted for elective reasons, less likely to have comorbid conditions, and more likely to require IMV for respiratory-related reasons (COPD, asthma), with fewer other organ involvement ($P < 0.05$ for all comparisons).

After multivariable adjustment, the odds of in-hospital mortality in morbidly obese patients receiving IMV were no different than non-obese patients (odds ratio [OR] 0.89; 95% CI, 0.74-1.06). The median hospital length of stay was about 1 day shorter in morbidly obese survivors compared to non-obese survivors ($P < 0.001$). Relative to non-obese patients receiving IMV, however, there was a stepwise increase in the risk of in-hospital mortality with an increasing number of organ failures in morbidly obese patients, which was significant once at least three organs (other than the respiratory system) were involved. Morbidly obese patients were significantly more likely to undergo tracheostomy (OR 2.19; 95% CI, 1.77-2.69). On the other hand, there were no significant differences in the proportion of morbidly obese patients requiring prolonged mechanical ventilation (> 96 hours), and they were more likely to be discharged to home, with or without home health care ($P < 0.05$), compared to non-obese patients.

### COMMENTARY

We have likely all taken care of morbidly obese patients and are familiar with the accompanying challenges surrounding their care: difficulties with invasive procedures and diagnostic testing (e.g., central line placement, intubation, CT scans), reduced thoraco-abdominal compliance resulting in difficulties with IMV and ventilator weaning, and limited cardiopulmonary reserve. The observations that morbidly obese patients were more likely to require IMV for COPD, asthma, or CHF exacerbations and more likely to undergo tracheostomy attest to some of the challenges in ventilating and gauging volume status in this patient population. Although this study does not show evidence of higher in-hospital mortality or length of stay in this population, as the authors point out, the morbidly obese patient being admitted to the hospital is often younger, more likely to be admitted for elective reasons,

and has, perhaps surprisingly, fewer comorbidities. Although these factors were accounted for in their multivariable analyses, the authors correctly acknowledge that this selection bias toward the "healthier" morbidly obese population may not have been completely removed in their adjustments.

The question of whether certain processes of care may confound some of the outcomes presented is an interesting one and should be explored further. Is adherence to protocols such as spontaneous breathing trials, low tidal volume ventilation, and interruption of sedation different when morbidly obese patients are involved? In some instances, we can hypothesize that nonadherence to these accepted practices may bias results toward worse outcomes in morbidly obese patients, but other areas may be murkier. For example, morbidly obese patients may be less likely to undergo daily spontaneous breathing trials or have sedation interrupted because they are perceived to be "higher risk" because of their body habitus, but these patients may be more likely to receive lower tidal volume ventilation because their measured plateau pressures underestimate actual transpulmonary pressures.

Given that currently one in three individuals is obese in the United States, it will be important to continue research efforts on this topic, especially if the trends of increasing percentages of morbidly obese patients who require hospitalization and IMV as seen in this study persist. ■

## ABSTRACT & COMMENTARY

# Adverse Effects of Deep Sedation in Mechanically Ventilated Patients

***By Linda L. Chlan, RN, PhD***

*Dean's Distinguished Professor of Symptom Management Research, The Ohio State University, College of Nursing*

**Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.**

SYNOPSIS: **Deep sedation during the early period of mechanical ventilatory support delays extubation and increases mortality, yet is a modifiable risk factor that requires innovative intervention to reduce these adverse outcomes.**

SOURCE: Shehabi Y, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: A prospective longitudinal multicenter cohort study. *Intensive Care Med* 2013;39:910-918.

This multicenter, prospective, longitudinal, observational, non-interventional cohort study was conducted in 11 Malaysian ICUs. This replication study aimed to determine if the findings from the Australian New Zealand Sedation Practice in Intensive Care Evaluation (ANZ SPICE) trial on sedation practice and depth of sedation would be similar in the participating Malaysian ICUs. The relationship among current sedation practices — depth of sedation (assessed every 4 hours with the Richmond Agitation and Sedation Scale [RASS]) after early initiation of mechanical ventilation, time to extubation, delirium (assessed daily with the Confusion Assessment Method for the ICU [CAM-ICU]) — and 180-day mortality were evaluated. All of the participating ICUs had 24/7 physician coverage (intensivist or anesthesiologist), with 1:2 nurse: patient ratios in most of the ICUs. Patients (n = 259) were included who had mechanical ventilation initiated within the previous 24 hours, were receiving sedative medications, and were expected to receive ventilatory support for > 24 hours. Deep sedation was defined as RASS ≤ -3. Patients were followed for up to 28 days in the ICU. The early ventilation period was defined as the first 48 hours of ventilatory support. All aspects of this replication study were modeled after the ANZ SPICE trial, including the statistical analyses that were performed at the Australian research center.

Overall, 180-day mortality was 46.4% with 8.5% of patients lost to follow-up. Midazolam was the most commonly used sedative medication (93%), administered to patients on almost 40% of study days. Dexmedetomidine was used in 29.3% of patients, while propofol was used in 28% of patients. Morphine was used slightly more (77.6%) than fentanyl (60.2%). The RASS assessments conducted in the first 48 hours of ventilatory support indicated that 58% of patients were deeply sedated, with 39.3% in the light range and 2.8% in the 2-4 RASS range. A small number of ICU days saw the use of neuromuscular blockade (4.1%), physical restraints (21.1%), or self-extubations (0.4%). A full 61% of patients were evaluated after 48 hours as still deeply sedated. Clinical reasons for desiring deep

sedation included controlled ventilation, muscle relaxation, and need to address severe agitation. Routine daily sedation interruption was implemented on only 2.3% of study days and was not a common practice in the Malaysian ICUs. Delirium was present overall in 44% of patients throughout the study period. In patients with > 8 days in the ICU, delirium was present in 50% of assessments, and increased to 68.9% in patients in the ICU ≥ 14 days.

Not surprisingly, patients who were initially deeply sedated had longer time to extubation with higher hospital and 180-day mortality. For every 4-hour assessment period spent at RASS -3 to -5, there was a 13% increase in risk of death at discharge, with an 8.5-hour delay in extubation, despite adjusting for sedative choice, diagnosis, and severity of illness. However, neither early deep sedation nor cumulative sedative medication doses were independent predictors of time to delirium. The Malaysian investigators concluded that their findings were similar to the ANZ SPICE trial findings and identified early, deep sedation as a potentially modifiable risk factor in delayed extubation and mortality. Shehabi et al suggest that early deep sedation may be a global problem associated with poor outcomes.

## ■ COMMENTARY

The findings of this replication study emphasize the deleterious effects of early, deep sedation on outcomes and mortality, regardless of the country of origin, something that appears to be a worldwide problem. Shehabi et al call for the delivery of interventions during the mechanical ventilatory support period to reduce the intensity and depth of sedation, particularly early in the ICU stay. However, this can be a very complicated, clinically vexing goal to attain.

Sedation management strategies need to be developed that allow mechanical ventilation synchrony and promote patient comfort, yet avoid deep patient sedation, unless medically indicated, at the same time. This may mean frequent ongoing evaluation of sedation goals, more than once daily during morning ICU rounds. The overall goal should be a comfortable, awake patient while achieving ventilator synchrony and adequate gas exchange. While this goal may not be achievable in all mechanically ventilated patients, it should be the target, nonetheless, given the mounting evidence that deep sedation does not provide any benefit to outcomes of this challenging and vulnerable group of ICU patients. ■

## CME/CNE Questions

**1. Palliative care is likely to be most effectively implemented using:**

a. the consultative model.
b. the integrative model.
c. interventions identified by an interdisciplinary care team.
d. interventions identified from patient care rounds.
e. a combination of the above.

**2. Compared to non-obese patients, morbidly obese patients receiving invasive mechanical ventilation (IMV):**

a. were more likely to be admitted through the emergency room.
b. had more comorbid conditions.
c. were more likely to receive IMV because of severe sepsis.
d. were mostly white.
e. were younger.

**3. Based on the studies summarized in this issue, the proportion of patients with acute respiratory failure due to acute exacerbations of COPD who receive noninvasive ventilation in U.S. hospitals is closest to:**

a. 15%.
b. 25%.
c. 35%.
d. 50%.
e. 75%.

**4. Which of the following statements best characterizes the methods used in the cohort replication study of early heavy sedation during mechanical ventilation?**

a. The ANZ SPICE trial was modeled after this trial conducted in the Malaysian ICUs.
b. The participating Malaysian ICUs were operated primarily by a central tele-ICU hub in Kuala Lumpur.
c. Deep sedation was the target sedation goal for patients overall.
d. The analyses were modeled after the ANZ SPICE protocol.

PHARMACOLOGY WATCH

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# Do Perioperative Beta-Blockers Reduce Mortality?

***In this issue:*** Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

## Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

## Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

## Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

## FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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## Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

**Source:** Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

The prevailing 5-year tamoxifen regimen for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

## Is There More Pro than Con in Probiotics in Critically Ill Adults?

**Source:** Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

The technical definition of probiotic offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

## Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

**Source:** Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

The recognition of obstructive sleep apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

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At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

## Inhaled Steroids Increase Risk of TB in COPD Patients

**Source:** Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

## The ASH Position Paper on Orthostatic Hypotension

**Source:** Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■

# CRITICAL CARE ALERT®

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


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