CRITICAL CARE
SCIENTIFIC UPDATE™

Reducing Iatrogenesis in the ICU: Delirium and Associated Complications in Critically Ill Patients

A review of presentations and discussion from the Critical Care Canada Forum

Toronto, Ontario November 13-16, 2011

Discussed by: Shannon Goddard, MD, FRCPC, and Eddy Fan, MD, FRCPC

Delirium is an important and common problem in the intensive care unit (ICU), representing a significant problem in terms of resource use, mortality, and long-term patient-important outcomes. Beyond the more intuitive challenges of caring for delirious patients in this setting, there is a growing understanding that delirium carries with it broader consequences, both during a patient's ICU stay and in the longer term. This issue of *Critical Care Scientific Update* outlines the "ABCDE" management approach – awakening, breathing trials, choice of sedation, delirium monitoring and treatment, and early mobilization – and the evidence supporting these interventions.

Historically, ICU care has focused on treating the underlying reason for admission, correcting aberrant physiology, and supporting patients while they recover from organ failure. Less attention has been paid to "back-end" ICU care, the care that is provided during the patient's recovery from critical illness. This phase of critical illness involves timely removal of unnecessary medical therapies, introduction of rehabilitation strategies, and the management of delirium.

Delirium is defined in the fourth edition (text revision) of the *Diagnostic and Statistical Manual* (DSM-IV-TR) as "a disturbance of consciousness and a change in cognition that develop over a short period of time".[1] The hallmark of delirium is inattention. It is often associated with psychomotor symptoms (both increased and decreased), perceptual disturbances, disordered sleep, and mood alterations. The DSM-IV further categorizes delirium according to etiology as either related to a general medical condition, substance-induced, or multifactorial. Clinicians have further characterized delirium in terms of the motor features as hyperactive, hypoactive, and mixed types.[2] These features may range from lethargy and restlessness through to agitation, hypervigilance, and combative behaviour. In contrast to hyperactive delirium, patients with hypoactive (or "quiet") delirium are lethargic, have markedly reduced motor activity and difficulty interacting with others or the environment.

The pathophysiology of delirium is not well understood. However, current literature suggests that alterations in neurotransmitters, cerebral blood flow, and integrity of the blood-brain barrier may play a role. Theories are emerging regarding the potential impact of conditions or risk factors associated with delirium (eg, sedation, sepsis) on these physiologic changes. For example, dynamic imaging studies show that cerebral blood flow is significantly impaired during acute delirium, leading to global cerebral hypoperfusion. This may help to explain the pathophysiological basis of some of the long-term consequences of delirium. In septic patients, the blood-brain barrier may be disrupted, leading to impaired capillary delivery of nutrients and oxygen to neuronal cells. Gamma-aminobutyric acid (GABA), a potent inhibitory neurotransmitter in the brain, is affected by many commonly used sedating medications (eg, benzodiazepines, propofol), and its reduction leads to unpredictable neuronal arousal. Investigating the role of sepsis in delirium is methodologically challenging, given the contributions of changing patient physiology, medical and surgical interventions, and the likely multifactorial nature of the process.

Acknowledgements:

Canadian Institutes of Health Research
Public Health Agency of Canada
John Granton, MD
Chair, Canadian Critical Care Society
John Marshall, MD
Chair, Canadian Critical Care Trials Group
Margaret Herridge, MD
Editor, *Critical Care Scientific Update*

The topics presented in *Critical Care Scientific Update* are independently determined and the content authored exclusively by physician-members of the Canadian Critical Care Society. *Critical Care Scientific Update* is made possible by unrestricted funding from the publisher, SNELL Medical Communication Inc., which receives educational grants from the pharmaceutical industry for the distribution of this publication.

It is estimated that 60%-80% of patients on mechanical ventilation and 40%-60% of ICU patients not on mechanical ventilation have delirium.[3-8] At first glance, these estimates may seem high, but this is probably due, in part, to significant underrecognition of delirium without daily monitoring in critically ill patients.[9] The diagnosis of delirium compels the clinician to focus on the bedside evaluation, and is easily missed without a directed assessment with validated instruments. In fact, a large study demonstrated that the majority of ICU patients suffer from mixed delirium (55%), followed by hypoactive delirium (43%), rather than a purely agitated delirium (2%), where physical agitation and outward confusion are clear.[10] Furthermore, hypoactive delirium may be missed in up to 75% of patients.[9]

The Consequences of Delirium

The association between delirium and worsening of patient-important outcomes has been well described in the literature, although the specific nature of that association is still being explored. This association may in part be explained by delirium as a marker for severity of illness; sicker patients get delirium and those same patients have poor outcomes. However, clinicians and researchers have become increasingly focused on the causal role delirium may play in the development of these outcomes.

Perhaps not surprisingly to front-line clinicians, ICU and hospital length of stay are both longer in patients with delirium,[5,11,12] with a resulting increase in hospital costs.[13] Importantly, delirium is associated with increased mortality, even beyond the hospital stay. In a prospective cohort study of mechanically ventilated ICU patients, those with delirium had a 3-fold increased risk of death at 6 months.[5] This relationship is more significant with greater duration of delirium.[14] Pisani et al[15] identified a 10% increased risk of death at one year for each day of delirium in the ICU.

There is also an important impact on long-term outcomes. Patients who suffer from delirium during their ICU stay are more likely to be discharged to another institution (eg, complex care facility) instead of home.[16] Long-term neurocognitive impairment has been demonstrated in prospective studies, both with self-reports[17] and objective testing.[18,19] Girard et al[20] found a significant association between duration of delirium and cognitive impairment at 3 and 12 months.

One challenge in studying these outcomes is the lack of baseline data on cognitive function. One large, prospective, cohort study of patients >65 years with normal baseline cognition looked at long-term neurocognitive outcomes based on acute care hospitalization (both ICU and non-ICU admissions). This study demonstrated that those with any hospital admission had a higher risk of incident dementia after discharge. Those admitted to the ICU had a 2-fold higher risk of dementia, but this was not statistically significant.[21] Furthermore, the small proportion of ICU patients among the total cohort raises the question of whether poor long-term outcomes in critically ill patients is simply a feature of illness requiring hospitalization.[22]

Finally, structural correlates of these impairments exist; survivors of acute respiratory distress syndrome have evidence of atrophy on brain computed tomography when compared to age-matched controls.[23]

Managing Delirium in a Complex Environment

The complex nature of delirium leads to significant underdiagnosis and undertreatment, and therefore requires a multimodal management approach. This approach must be integrated with other treatment goals and priorities in the critical care environment and supported, whenever possible, by the best existing published evidence. One approach to integrating delirium management into other best practices is the "ABCDE" approach.[24] The ABCDE approach consists of 5 basic evidence-based interventions (See Table 1), which are focused on integrating liberation from mechanical ventilation with awakening and rehabilitating ICU patients.

A – Awakening

It has become clear that deep sedation by continuous intravenous infusion leads to delayed extubation and prolonged ICU stay.[25,26] A landmark study by Kress et al[25] demonstrated shorter median durations of mechanical ventilation (4.9 versus 7.3 days; P=0.004) and ICU length of stay (6.4 versus 9.9 days; P=0.02) in patients who received daily sedative interruptions compared with "usual care."

Despite this compelling evidence, this intervention has been difficult to implement in many centres. The use of any sedation protocol is low in most chart reviews.[27-29] Even in clinician self-reporting studies, daily sedation interruption is infrequent.[30] Healthcare providers routinely cite concern about device removal, compromise of patient comfort, and compromised respiratory status as reasons why daily sedation is not interrupted.[31] However, in the study by Kress et al,[25] the incidence of complications (eg, self-extubation) was not different between groups (4% in the daily interruption group versus 7% among controls; P=0.88).

Several studies have demonstrated an association between the risk of delirium and the use of sedatives and analgesic medications, particularly benzodiazepines.[32-34] Thus, reduction in the amount of sedation and analgesia use may improve the risk of developing delirium.

B – Breathing trials

Liberation from mechanical ventilation is a key goal for most ICU patients. Endotracheal tubes and ventilators contribute to delirium, increase sedation and pose a barrier to nursing care and physical therapy. Performing routine daily spontaneous breathing trials (SBTs) on mechanically ventilated patients leads to a significant reduction in median duration of mechanical ventilation (4.5 versus 6 days, P=0.004).[35] When daily sedation interruption and SBTs are combined, there appears to be further reduction in the duration of

Table 1: The ABCDE Approach to Delirium Management[60]	
A – Awakening (daily)	Interruption of sedation, with subsequent reduction by half if patient cannot be extubated
B – Daily spontaneous breathing trial	Should occur concurrently with daily awakening
C – Choice of sedation	Avoid benzodiazepines, which may contribute to delirium Consider use of alpha-2 agonists (eg, clonidine, dexmedetomidine).
D – Delirium assessment	Use validated scale (eg, CAM-ICU or ICDSC) to assess daily for presence of delirium
E – Exercise/ early mobility	Institute a program for early mobility for all ICU patients

CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit

mechanical ventilation, as measured by ventilator-free days as compared to usual sedation practices and daily SBTs (mean difference 3.1 days, 95% confidence interval [CI] 0.7 to 5.6; *P*=0.02).[4] However, SBTs are not being routinely performed in daily clinical practice, and along with sedative interruptions, represent important targets for quality improvement in the ICU.[36,37]

C – Choice of sedation

Traditionally, sedation in the ICU has focused on GABA-active agents, such as benzodiazepines and propofol, likely because these were the most available agents. In a review of sedation and analgesia practices from around the world, Mehta et al[30] noted that in every survey, midazolam (or benzodiazepines in general) and propofol were cited as the most frequent agents. However, there is an evolving body of literature showing that non-GABA active agents may be better and that sedating agents should not be used in lieu of appropriate analgesia.

Dexmedetomidine is a novel alpha-2 agonist that has both sedative and analgesic effects, without significant respiratory depression, making it a well-suited drug for ICU sedation.[38] Four large, randomized, controlled trials have compared dexmedetomidine to lorazepam,[6] midazolam,[39,40] or propofol[40] for sedation. In the first study (MENDS trial), patients on dexmedetomidine had 4 fewer days of delirium or coma than those on lorazepam (median 3 versus 7 days; *P*=0.01). Similarly, in the second study (SEDCOM trial), patients treated with dexmedetomidine had equal levels of sedation, but less delirium (difference, 22.6%; 95% CI, 14% to 33%). They also had a shorter time to extubation, although ICU length of stay was similar. Finally, in the MIDEX and PRODEX trials, dexmedetomidine was associated with significantly shorter median duration of mechanical ventilation as compared to midazolam (123 versus 164 hours; *P*=0.03) but not propofol (97 versus 118 hours; *P*=0.24); however, dexmedetomidine was associated with significantly more hypotension and bradycardia than midazolam. It is important to note that these trials do not tell us whether the observed improvement in delirium is related to the dexmedetomidine or to avoidance of benzodiazepines.

Addressing pain in ICU patients is an important component of delirium prevention and management. In some cases, opioids, which may result in sedation, may be used to manage delirium when the cause of the delirium is pain. For example, in a study of burn patients suffering from significant pain, benzodiazepines increased the risk of delirium while opioids were protective.[41] Finally, in a randomized study comparing "no sedation" (prioritizing analgesia with morphine boluses and without infusions of sedative or analgesics) as compared to sedation with daily interruption, agitated delirium was more frequent in the no sedation group (20 versus 4%; *P*=0.04), but the differences may have been due to difficulties in detecting delirium in the daily interruption group, who may have been more sedated.[42]

D - Delirium monitoring and treatment

As mentioned previously, underdiagnosis of delirium is a significant problem, particularly among patients suffering predominantly from the hypoactive form.[9] Active screening detects delirium at a prevalence of 60%-80%.[3-8]

Screening for delirium is a 2-step process that requires first assessing the level of sedation/arousal, then screening for delirium using a validated instrument. For daily assessments of sedation/arousal level, one of several well-known tools may be used, including the Sedation-Agitation Scale (SAS), Ramsay Scale, or the Richmond Agitation-Sedation Scale (RASS); examples are available at www.icudelirium.org. The RASS scale has excellent inter-rater reliability and criterion, construct, and face validity,[43,44] and is useful for following patients over time. Subsequent to an assessment of sedation/arousal, a specific delirium assessment tool should be employed. Two commonly used instruments are the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Table 2), both of which have been shown to have good sensitivity and specificity.[45,46]

Once delirium has been identified, the clinician can focus on management. The first priority in managing delirium should be identification and treatment/reversal of underlying causes. A memory guide or mnemonic may be useful to remind clinicians of common causes of delirium (Table 3). Commonly, infection or sepsis may cause or contribute to delirium. Medical interventions such as sedation with benzodiazepines, physical restraints, or intubation may play a role. Once those issues have been minimized, nonpharmacological interventions may be employed. Currently, the best nonpharmacological intervention shown to reduce delirium is early mobilization, although the evidence is limited to

Table 2: Delirium Screening Tools		
	CAM-ICU[45]	**ICDSC**[46]
Criteria	1. Acute onset or fluctuating course 2. Inattention 3. Disorganized thinking 4. Altered level of consciousness	1. Inattention 2. Disorientation 3. Hallucination-delusion-psychosis 4. Psychomotor agitation or retardation 5. Inappropriate speech or mood 6. Sleep/wake cycle disturbance 7. Symptom fluctuation
Scoring	The patient is determined to be delirious if he/she manifests both features 1 and 2, plus either feature 3 or 4.	The checklist is completed based on information collected from each entire 8-hour shift or from previous 24 hours. Each item can be scored 1 for obvious manifestations, or 0 for no manifestation or no assessment possible. A score of ≥4 points indicates delirium.

medical ICU patients.[47] Beyond this, no high-quality data exist; however, noninvasive strategies such as constant patient reorientation, correction of sensory deficits (eg, eye glasses, hearing aids), and sleep protocols have been described.[48]

Pharmacological treatments for delirium are not well established. As described earlier, dexmedetomidine may have benefit, although its role may be in avoiding other deliriogenic agents rather than it being a specific treatment for delirium. Antipsychotic agents are often used, although there are limited and conflicting data regarding their use in the treatment of delirium. Only one clinical trial has compared typical antipsychotics to placebo in ICU patients as delirium prevention. This feasibility study found no difference in days alive without delirium or coma in a 3-group, double-blind, randomized trial of haloperidol versus ziprasidone versus placebo.[49] Extrapyramidal side effects were rare in all groups. The results of this pilot study formed the basis of ongoing Modifying the Impact of ICU-Associated Neurologic Dysfunction (MIND)-USA randomized, controlled trial (ClinicalTrials.gov NCT01211522), which will evaluate the potential role of haloperidol and/or ziprasidone in the management of delirium. A few trials examined the effects of atypical antipsychotics. Skrobik et al[50] compared olanzapine to haloperidol for the treatment of ICU delirium, and found no difference in delirium symptoms between the 2 groups, although more extrapyramidal symptoms were seen in the haloperidol group. Conclusions from this trial are limited by its small sample size (73 patients) and the lack of blinding among clinicians participating in the study. More recently, Devlin et al[51] compared quetiapine to placebo in ICU patients already receiving as-needed haloperidol. Patients receiving quetiapine demonstrated shorter times to first resolution of delirium (1.0 versus 4.5 days; P=0.001), and a shorter duration of delirium (36 versus 120 hours; P=0.006). Again, the results of this study are limited by its small sample size (36 patients) and require confirmation in a large, randomized controlled trial. Importantly, none of these clinical trials demonstrated any serious adverse events from the use of antipsychotics in the management of delirium.

At this time, there is no literature to support the routine use of antipsychotics for delirium prophylaxis in critically ill patients. Interestingly, a randomized, placebo-controlled trial in 430 elderly hip surgery patients demonstrated no impact of haloperidol (started preoperatively and continued for 3 days postoperatively) on the incidence of delirium (16% in both groups); however, it significantly reduced the severity and duration of delirium, without increased adverse events.[52] Future studies are needed to evaluate the efficacy and safety of antipsychotics for the prevention and treatment of delirium in the ICU, as well as its potential impact on long-term outcomes in survivors of critical illness.

E – Early mobilization

A number of studies have shown that early mobilization is both safe and feasible in mechanically ventilated patients.[53-57] One randomized trial demonstrated that when paired with sedative interruption and SBTs, patients who were part of an early rehabilitation protocol were more likely to achieve functional independence at hospital discharge (odds ratio 2.7; P=0.02).[47] Interestingly, patients in the intervention arm also had a shorter

Table 3: The THINK Mnemonic for Diagnosis of Etiology of Delirium[48]	
T	Toxic situations – Congestive heart failure, shock, dehydration, deliriogenic medications (tight titration), new organ failure (eg, acute kidney injury, liver failure)
H	Hypoxemia
I	Infection/sepsis (nosocomial), Immobilization
N	Nonpharmacological interventions – Hearing aids, glasses, reorientation, sleep protocols, music, noise control, early rehabilitation
K	K^+ (potassium) or electrolyte problems

duration of delirium (2 versus 4 days; P=0.01). Oversedation and delirium are important barriers to early rehabilitation.[57,58] Strategies outlined above to aggressively limit oversedation and the duration and severity of delirium may increase the number of, and rapidity at which, patients in the ICU may become eligible for physical and occupational therapy.[59] Finally, although these data are promising, these studies have focused on patients admitted to medical ICUs and these results have not been replicated in other critically ill populations (eg, surgical, trauma, neurological, or mixed ICUs).

Conclusion

Delirium is a highly prevalent disorder in the ICU, with significant implications for both in-hospital and long-term outcomes. It is significantly associated with prolonged ICU length of stay, long-term neurocognitive impairment, and increased mortality. The diagnosis can be subtle, particularly when patients have the hypoactive subtype. Thus, accurate and timely diagnosis requires active screening at the bedside with validated tools. Traditional strategies of deep sedation and immobilization are gradually being replaced with a culture of the awake, calm, cooperative, and mobile ICU patient. The "ABCDE" approach combines multiple evidence-based interventions into a logical, intuitive, and accessible protocol that can be used by healthcare professionals of different backgrounds in different settings to approach delirium management within a holistic framework designed to improve both short- and long-term outcomes in critically ill patients.

Many unanswered questions on the prevention and management of delirium remain, including the optimal pharmacological and nonpharmacological strategies for the management of delirium. A better understanding of the risk factors and mechanisms for the development of delirium in the ICU, as well as their link to long-term neurocognitive and neuropsychiatric sequelae, will help to uncover new targets for potential interventions. Careful attention to limiting "intensive" care when it is no longer needed or helping our patients may help to get them out of the ICU and hospital sooner, with mind and body intact. *Primum non nocere*.

Dr. Goddard *is a Postgraduate Trainee, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario.* ***Dr. Fan*** *is an Assistant Professor of Medicine, Interdepartmental Division of Critical Care Medicine, University of Toronto, and an Intensivist, Toronto General and Mount Sinai hospitals, Toronto, Ontario.*

References

1. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR). Arlington,VA: American Psychiatric Association Press; 2000.
2. Lipowski ZJ. Delirium in the elderly patient. *N Engl J Med*. 1989;320(9):578-582.
3. Fraser GL, Prato BS, Riker RR, Berthiaume D, Wilkins ML. Frequency, severity, and treatment of agitation in young versus elderly patients in the ICU. *Pharmacotherapy*. 2000;20(1):75-82.
4. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
5. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753-1762.
6. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298(22):2644-2653.
7. Micek ST, Anand NJ, Laible BR, Shannon WD, Kollef MH. Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. *Crit Care Med*. 2005;33(6):1260-1265.
8. Lat I, McMillian W, Taylor S, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. *Crit Care Med*. 2009;37(6):1898-1905.
9. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med*. 2009;35(7):1276-1280.
10. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. 2006;54(3):479-484.
11. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med*. 2001;27(12):1892-1900.
12. Thomason JWW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care*. 2005;9(4):R375-R381.
13. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. 2004;32(4):955-962.
14. Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med*. 2010;38(12):2311-2318.
15. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009;180(11):1092-1097.
16. Nelson JE, Tandon N, Mercado AF, Camhi SL, Ely EW, Morrison RS. Brain dysfunction: another burden for the chronically critically ill. *Arch Intern Med*. 2006;166(18):1993-1999.
17. Adhikari NKJ, McAndrews MP, Tansey CM, et al. Self-reported symptoms of depression and memory dysfunction in survivors of ARDS. *Chest*. 2009;135(3):678-687.
18. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171(4):340-347.
19. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
20. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38(7):1513-1520.
21. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA*. 2010;303(8):763-770.
22. Rubenfeld GD. Does the hospital make you older faster? *Am J Respir Crit Care Med*. 2012;185(8):796-798.
23. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of Acute Respiratory Distress Syndrome. *Brain Inj*. 2006;20(3):263-271.
24. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the "ABCDE" approach. *Curr Opin Crit Care*. 2011;17(1):43-49.

25. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
26. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest*. 1998;114(2):541-548.
27. Payen J-F, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology*. 2007;106(4):687-695.
28. Martin J, Franck M, Sigel S, Weiss M, Spies C. Changes in sedation management in German intensive care units between 2002 and 2006: a national follow-up survey. *Crit Care*. 2007;11(6):R124.
29. Ramaswamy S, Rangappa D, Wheatley E. National survey on current practice of sedation and analgesia in intensive care in United Kingdom. *Int Care Med*. 2009 Oct. 11;22nd ESICM Annual Congress.
30. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med*. 2006;34(2):374-380.
31. Tanios MA, Nevins ML, Hendra KP, et al. A randomized, controlled trial of the role of weaning predictors in clinical decision making. *Crit Care Med*. 2006;34(10):2530-2535.
32. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-26.
33. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65(1):34-41.
34. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med*. 2009;37(1):177-183.
35. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335(25):1864-1869.
36. Kahn JM, Brake H, Steinberg KP. Intensivist physician staffing and the process of care in academic medical centres. *Qual Saf Health Care*. 2007;16(5):329-333.
37. Burns KEA, Lellouche F, Loisel F, et al. Weaning critically ill adults from invasive mechanical ventilation: a national survey. *Can J Anaesth*. 2009;56(8):567-576.
38. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. *Am J Respir Crit Care Med*. 2012;185(5):486-497.
39. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-499.
40. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151-1160.
41. Agarwal V, O Neill PJ, Cotton BA, Pet al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res*. 2010;31(5):706-715.
42. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475-480.
43. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-2991.
44. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.
45. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703-2710.
46. Bergeron N, Dubois M-J, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001;27(5):859-864.
47. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.
48. icudelirium.org. Available at: http://www.mc.vanderbilt.edu/icudelirium/overview.html. Accessed on April 9, 2012.
49. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Crit Care Med*. 2010;38(2):428-437.
50. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. 2004;30(3):444-449.
51. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38(2):419-427.
52. Kalisvaart KJ, De Jonghe JFM, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. 2005;53(10):1658-666.
53. Bailey PP, Miller RR, Clemmer TP. Culture of early mobility in mechanically ventilated patients. *Crit Care Med*. 2009;37(10 Suppl):S429-S435.
54. Bourdin G, Barbier J, Burle JF, et al. The feasibility of early physical activity in intensive care unit patients: a prospective observational one-center study. *Respir Care*. 2010;55(4):400-407.
55. Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci*. 2011;341(5):373-377.
56. Needham DM, Korupolu R. Rehabilitation quality improvement in an intensive care unit setting: implementation of a quality improvement model. *Top Stroke Rehabil*. 2010;17(4):271-281.
57. Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med*. 2010;38(11):2089-2094.
58. Zanni JM, Korupolu R, Fan E, et al. Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project. *J Crit Care*. 2010;25(2):254-262.
59. Fan E. What is stopping us from early mobility in the intensive care unit? *Crit Care Med*. 2010;38(11):2254-2255.
60. Vasilevskis EE, Ely EW, Speroff T, Pun BT, Boehm L, Dittus RS. Reducing iatrogenic risks: ICU-acquired delirium and weakness–crossing the quality chasm. *Chest*. 2010;138(5):1224-1233.

Disclosure: *Dr. Goddard has stated that she has no disclosures to report in association with the contents of this issue. Dr. Fan is supported by a Fellowship Award from the Canadian Institutes of Health Research (CIHR), and is the Co-Principal Investigator for a Delirium Quality Improvement project funded by an unrestricted grant from Hospira Corporation.*

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Hospira Healthcare Corporation to support the distribution of this issue of *Critical Care Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Canadian Critical Care Society, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party. The views expressed in this publication do not necessarily reflect those of the Canadian Critical Care Society.