Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

E. Wesley Ely, MD, MPH
Ayumi Shintani, PhD, MPH
Brenda Truman, RN, MSN
Theodore Speroff, PhD
Sharon M. Gordon, PsyD
Frank E. Harrell, Jr, PhD
Sharon K. Inouye, MD, MPH
Gordon R. Bernard, MD
Robert S. Dittus, MD, MPH

Context In the intensive care unit (ICU), delirium is a common yet underdiagnosed form of organ dysfunction, and its contribution to patient outcomes is unclear.

Objective To determine if delirium is an independent predictor of clinical outcomes, including 6-month mortality and length of stay among ICU patients receiving mechanical ventilation.

Design, Setting, and Participants Prospective cohort study enrolling 275 consecutive mechanically ventilated patients admitted to adult medical and coronary ICUs of a US university-based medical center between February 2000 and May 2001. Patients were followed up for development of delirium over 2158 ICU days using the Confusion Assessment Method for the ICU and the Richmond Agitation-Sedation Scale.

Main Outcome Measures Primary outcomes included 6-month mortality, overall hospital length of stay, and length of stay in the post-ICU period. Secondary outcomes were ventilator-free days and cognitive impairment at hospital discharge.

Results Of 275 patients, 51 (18.5%) had persistent coma and died in the hospital. Among the remaining 224 patients, 183 (81.7%) developed delirium at some point during the ICU stay. Baseline demographics including age, comorbidity scores, dementia scores, activities of daily living, severity of illness, and admission diagnoses were similar between those with and without delirium ($P>.05$ for all). Patients who developed delirium had higher 6-month mortality rates (34% vs 15%, $P=.03$) and spent 10 days longer in the hospital than those who never developed delirium ($P<.001$). After adjusting for covariates (including age, severity of illness, comorbid conditions, coma, and use of sedatives or analgesic medications), delirium was independently associated with higher 6-month mortality (adjusted hazard ratio [HR], 3.2; 95% confidence interval [CI], 1.4-7.7; $P=.008$), and longer hospital stay (adjusted HR, 2.0; 95% CI, 1.4-3.0; $P<.001$). Delirium in the ICU was also independently associated with a longer post-ICU stay (adjusted HR, 1.6; 95% CI, 1.2-2.3; $P=.009$), fewer median days alive and without mechanical ventilation (19 [interquartile range, 4-23] vs 24 [19-26]; adjusted $P=.03$), and a higher incidence of cognitive impairment at hospital discharge (adjusted HR, 9.1; 95% CI, 2.3-35.3; $P=.002$).

Conclusion Delirium was an independent predictor of higher 6-month mortality and longer hospital stay even after adjusting for relevant covariates including coma, sedatives, and analgesics in patients receiving mechanical ventilation.

JAMA. 2004;291:1753-1762 www.jama.com

In the United States, 55 000 patients are cared for daily in more than 6 000 intensive care units (ICUs).[1] The most common reason for ICU admission is respiratory failure and the need for a mechanical ventilator.[2] Although hospital mortality for such patients ranges from 30% to 50%,[3] only 16% of patients receiving mechanical ventilation die directly of respiratory failure.[4] In fact, nonpulmonary acute organ dysfunction contributes importantly to mortality.[5,6] Delirium is one of these nonpulmonary considerations yet remains understudied in critically ill patients. Although scoring systems for severity of illness have included the Glasgow Coma Scale[7,8] as an important predictor of outcome, there has been no in-depth analysis focusing on the direct contribution of delirium to clinical outcomes in critically ill ICU patients.

Management of patients with sepsis and multiorgan failure has tradition-

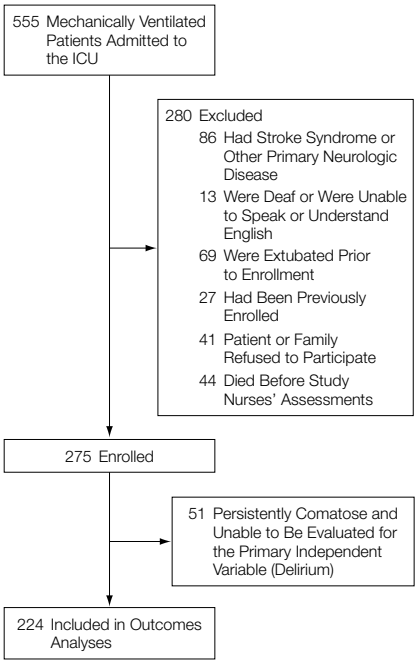
See also Patient Page.

Author Affiliations are listed at the end of this article.
Corresponding Author: E. Wesley Ely, MD, MPH, Division of Allergy/Pulmonary/Critical Care Medicine, Center for Health Services Research, Sixth Floor Medical Center East #6109, Vanderbilt University Medical Center, Nashville, TN 37232-8300 (wes.ely@vanderbilt.edu; www.icudelirium.org).
Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.
Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD; Adrienne Randolph, MD.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

Figure 1. Flow of Patients in Study Cohort



ICU indicates intensive care unit.

ally been centered on dysfunction in the heart, lungs, or kidneys rather than the brain, though the brain is one of the organs most commonly involved.[9-13] Delirium has received little attention in ICU settings because it is (1) rarely a primary reason for admission, (2) often believed to be iatrogenic due to medications, (3) frequently explained away as "ICU psychosis," and (4) believed to have no adverse consequences in terms of patients' ultimate outcome.[14-16] Last, there is a paucity of published trials of prevention or treatment of delirium showing altered outcomes[17] and none in ICU patients.

Even among clinicians who exhibit an overall appreciation for delirium as an important form of organ dysfunction, recent data point to a general disconnect between its perceived importance and current monitoring practices. Despite recent guidelines suggesting that ICU patients be monitored daily for delirium,[18] only 6.4% (58/912) of critical care professionals surveyed in 2001-2002 reported objectively monitoring for this condition.[19] Indeed, delirium, especially the hypoactive subtype,[20,21] goes unrecognized in more than two thirds of the patients in clinical practice.[22-25]

The original Confusion Assessment Method of Inouye et al[26] popularized monitoring of delirium by nonpsychiatrists. In non-ICU hospital settings, delirium has been associated with prolonged stay, greater dependency, subsequent institutionalization, and increased mortality.[17,27-34] However, only recently have valid and reliable instruments to measure both level of arousal[35-37] and delirium[38-40] in ICU patients become available. Using these instruments, our pilot study showed that delirium in the ICU was an important determinant of length of hospital stay.[41] We undertook the current study to test the hypothesis that delirium in the ICU is an independent predictor of 6-month mortality and length of stay among patients receiving mechanical ventilation even after adjusting for other covariates.

METHODS

Patients

The Vanderbilt University institutional review board approved this study, and written informed consent was obtained from patients or their surrogates. Enrollment criteria included any adult, mechanically ventilated patient admitted to medical or coronary ICUs of the 631-bed Vanderbilt University Medical Center between February 2000 to May 2001. While no outcomes data from this report have been previously published, other data from this cohort have been published.[37,39,42] Exclusion criteria, defined a priori, are outlined in the patient flow diagram (FIGURE 1).

Study Protocol

Study nurses enrolled patients each morning and recorded baseline demographic information. Information collected at enrollment included patient demographics and severity of illness using the most abnormal values obtained during the first 24 hours of ICU stay to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) (scale range, 0-71)[7] and Sequential Organ Failure Assessment (SOFA) (scale range, 0-24) scores.[8] The Charlson Comorbidity Index, which represents the sum of a weighted index that takes into account the number and seriousness of preexisting comorbid conditions, was calculated as per Deyo et al.[43] Surrogate assessments were used for baseline activities of daily living (scale range, 0-12),[44] visual and hearing deficits, and the modified Blessed Dementia Rating Scale (mBDRS) (scale range, 0-17),[45] an instrument validated against brain pathological specimens to measure a patient's baseline likelihood of dementia.

Terminology

Delirium has more than 25 synonyms, including acute encephalopathy, septic encephalopathy, toxic psychosis, ICU psychosis, and acute confusional state.[10,11,14,46,47] Delirium will be the term used herein, because the neurologic monitoring instrument used in this investigation (described below) was developed and validated using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for delirium.[48]

Explanatory Variable

Definitions and Patient Assessments. Patients' neurologic status was assessed daily by the study nurses and defined as normal, delirious, or comatose using a 1- to 2-minute neurologic assessment that objectively measured patients' arousal and delirium status. Arousal was measured using the Richmond Agitation-Sedation Scale (RASS).[36,37] The RASS is a well-validated and highly reliable 10-point scale with scores from +1 to +4 assigned for levels of agitation through combativeness, 0 assigned for alert and calm state, and –1 to –5 assigned for successive levels of depressed arousal or coma.[37] Delirium, the independent variable, was measured using a well-validated and highly reliable instrument, the Confusion Assessment Method for the ICU (CAM-ICU).[39,40] The CAM-ICU assessment was positive if patients demonstrated an acute change or fluctuation in the course of

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

their mental status (as determined by abnormalities or fluctuations in the RASS scores), plus inattention and either disorganized thinking or an altered level of consciousness.[39,40] By definition, patients were *delirious* if they responded to verbal stimulation with eye opening (RASS scores of –3 to +4) and had positive CAM-ICU assessments. Patients were defined as *comatose* if they responded only to physical/painful stimulation with movement but had no eye opening (RASS score, –4) or if they had no response to verbal or physical stimulation (RASS score, –5). Patients were defined as *normal* if they were not delirious or comatose.

Categorization by Explanatory Variable. Using daily assessments described above, it was determined a priori that patients would be included in a "delirium" group if they ever had delirium while in the ICU, and all others would be included in a "no delirium" group. To understand the phenomenology of these groups, patients in the delirium group were further categorized as "delirium only" (ie, delirium but no episodes of coma) or as "delirium-coma" (ie, delirium and coma). Likewise, patients in the no delirium group were categorized as "normal" (ie, no episodes of delirium or coma) or as "coma-normal" (ie, transient coma [eg, coma due to sedative medications] followed by consistently normal examinations). Patients who were comatose on all ICU evaluations during the study were categorized as "persistent coma."

Outcome Variables

The primary outcome variables included 6-month mortality, overall hospital length of stay, and length of stay in the post-ICU period. In addition, we included 2 secondary outcome variables: ventilator-free days and cognitive impairment at discharge. Ventilator-free days were defined as the number of days alive and free of mechanical ventilation between study enrollment and day 28.[49] Cognitive impairment at discharge was defined as a Mini-Mental State Examination score[50] of less than 24 out of a possible 30 points.[51-53]

Statistical Analysis

Patients' baseline demographic and clinical variables were assessed using Wilcoxon rank sum tests for continuous variables; Fisher exact tests were used for comparing proportions. For analysis of analgesics (morphine, fentanyl) and sedatives (lorazepam, propofol), mean daily ICU dose and cumulative dose per patient during the ICU stay were used as summary measures. Administered benzodiazepines were either lorazepam or midazolam, and midazolam dose was converted to "lorazepam equivalents" (henceforth referred to as lorazepam) by dividing by 3 to achieve equipotent dose.[54] Wilcoxon rank sum tests were used to compare distributions of the drugs between the no delirium and delirium groups.

Six-month mortality, overall hospital length of stay, and length of stay after first ICU discharge were analyzed using time-to-event analyses. Patients were followed up from time of enrollment until hospital discharge. All survivors were then followed up using the hospital's electronic record system, monthly telephone calls, and in-person visits for survival status. Kaplan-Meier survival curves were used for graphical presentation of time to death or hospital discharge, and log-rank statistics were used to assess difference by overall delirium status.[55] For 6-month mortality analyses, patients were censored at the time of last contact alive or at 6 months from enrollment, whichever was first. Censoring for length-of-stay analyses occurred at time of hospital death.

Cox proportional hazard regression models with time-dependent covariates[56-58] were used to obtain hazard ratios (HRs) of death up to 6 months from enrollment and HRs of remaining in hospital. Details of the model construction are described below. The 11 covariates in the multivariable Cox regression models included a time-dependent coma variable, 6 additional baseline covariates chosen a priori based on clinical relevance (patient age at enrollment, Charlson Comorbidity Index,[43] mBDRS score,[45] APACHE II score,[7] SOFA score,[8,59,60] admitting diagnoses of sepsis or acute respiratory distress syndrome), and the 4 sedative and analgesic medications used in this cohort (lorazepam, propofol, morphine, and fentanyl). Patients' neurologic status (normal, delirious, comatose) was updated daily in the ICU, and time-dependent variables were used for delirium and coma separately. This time-dependent delirium incidence variable was coded as 0 for the days prior to the first delirious event, and coded as 1 thereafter. The time-dependent coma incidence variable was coded similarly.

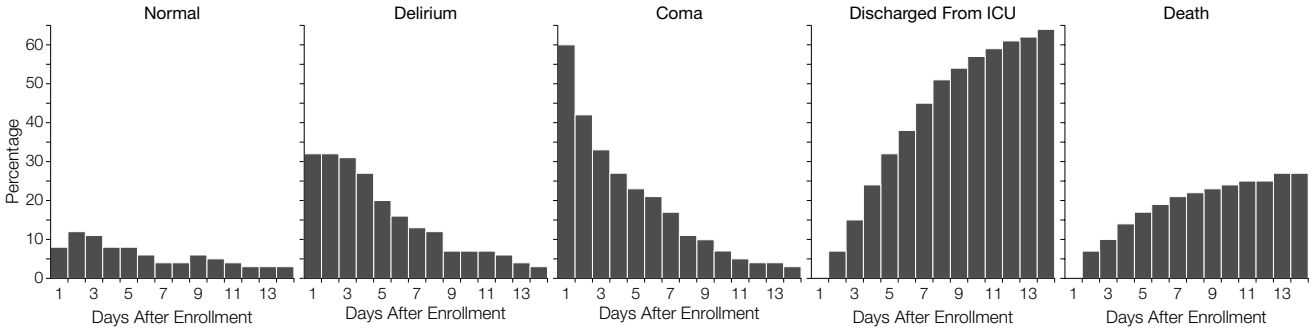
In addition, we performed a similar analysis that considered the duration of delirium using cumulative number of days of delirium, coding the time-dependent delirium duration variable as 0 until a delirium event occurred, and then incrementally adding 1 when each additional day of delirium occurred. The time-dependent coma duration variable was created similarly for this additional analysis.

The time-dependent delirium incidence variable was used as the main independent variable in all Cox models with adjustment for time-dependent coma incidence variable. Cox regression models were then used to further control for the additional 6 baseline covariates mentioned above and the 4 sedative and analgesic medications. Dummy coding was used for missing observations with the mBDRS. Because coma was already being handled as a covariate in the model, the APACHE II and SOFA scores were calculated without inclusion of the Glasgow Coma Scale. To incorporate sedative (lorazepam, propofol) and analgesic (morphine, fentanyl) medications in a time-dependent fashion, daily use of medication was coded as 1 for each of 4 drug variables separately if any amount was administered prior to daily assessment of neurologic status and was coded as 0 otherwise. In an additional analysis, time-dependent cumulative dose of sedatives and narcotics were incorporated into the model. Collinearity among all independent variables was evaluated by examining the variance in-

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

Figure 2. Daily Neurologic Status of 275 Patients in the ICU, Through the First 14 Days of the Study



Denominator is identical (N = 275) for all 14 days. ICU indicates intensive care unit.

flation factor.[61] Assumptions of proportional hazard for the final models were evaluated by examining interactions between time and each variable in the model. When significant interactions were found, those interaction terms were included in the final model.

Ventilator-free days were calculated as described in the "Dependent Variables" section above and compared between the delirium and no delirium groups. A Poisson regression model with overdispersion correction was used to control for the set of covariates stated above. Presence or absence of cognitive impairment at hospital discharge was assessed as described in the "Dependent Variables" section and compared between the delirium and no delirium groups using Fisher exact tests, and a logistic regression model was used to adjust for the set of 11 covariates. All data analyses were performed using SAS 8.02 (SAS Institute, Cary, NC); a significance level of .05 was used for statistical inferences.

RESULTS

Patients' Baseline Characteristics

During the study period, 555 mechanically ventilated ICU patients were admitted, of whom 275 (49.5%) were enrolled within a mean and median of 1 day and 280 met exclusion criteria (Figure 1). On enrollment, 23 (8.4%) patients were defined as normal, 89 (32.4%) as delirious, and 163 (59.3%) as comatose. FIGURE 2 shows the proportion of patients in each neurologic category (as well as death or ICU discharge) over the first 14 days from study enrollment. Of the 275 enrolled patients, 51 (18.5%) never woke up from coma and experienced 100% ICU mortality after a median of 3 (interquartile range [IQR], 1-5) days. These 51 patients with persistent coma had a mean age of 55 (SD, 16) years and similar baseline characteristics compared with the remaining 224 patients, with the exception of greater severity of illness at enrollment as measured by mean APACHE II scores (29.5 [SD, 9]) and SOFA scores (12.1 (SD, 3.8]) and by greater rates of malignancy (14%) and sepsis/acute respiratory distress syndrome (63%) as admission diagnoses ($P<.05$ for all). Due to their 100% mortality and the inability to evaluate them for the independent variable (delirium), patients categorized as experiencing persistent coma were not included in outcomes analyses. The remaining 224 patients were used for these analyses; their baseline characteristics are shown in TABLE 1. The cohort was divided into 2 groups according to whether they ever developed delirium in the ICU. There were no significant differences between the delirium and no delirium groups for demographic variables, baseline comorbidities, activities of daily living, severity-of-illness scores, organ dysfunction scores, or admission diagnoses.

Prevalence of Delirium and Coma

All 224 patients were followed up for development of delirium over 2158 ICU days. Forty-one patients (18.3%) never demonstrated delirium in the ICU (ie, the no delirium group); of those, 24 (58.5%) were in a coma for a median of 1.5 (IQR, 1-3) days, during which time 21 (87.5%) received sedative or analgesic medications. Delirium in the ICU developed in 183 (81.7%) patients (ie, the delirium group) for a median of 2 (IQR, 1-3) days, of whom 123 also were in a coma for a median of 2 (IQR, 1-4) days. Delirium occurred in 77.9% (60/77) of those without coma and in 83.7% (123/147) of those with coma ($P=.29$). Overall, patients spent 21.6% of their ICU days as normal, 43.1% as delirious, and 35.3% as comatose. Of patients who were alert or easily arousable as measured by a RASS score of 0 or –1, more than half (54.5%) were delirious.

Sedative and Analgesic Medication Use

Mean daily dose and cumulative administered dose of sedative and narcotic medications (ie, lorazepam, propofol, morphine, and fentanyl) used in this cohort are presented in TABLE 2. Both mean daily and cumulative doses of these medications were higher in patients in the delirium group, but only lorazepam was significantly different between the 2 groups.

Delirium and Associated Clinical Outcomes

Six-Month Mortality. During the 6-month follow-up period, 34% (63/183) of the patients in the delirium group

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

died vs 15% (6/41) of the patients in the no delirium group ($P=.03$) (TABLE 3). FIGURE 3A shows Kaplan-Meier curves of survival to 6 months among the patients in both groups, with significantly higher mortality among patients with delirium in the ICU. Figure 3B further depicts the patients' survival according to both delirium and coma status.

Using a time-dependent multivariable Cox proportional hazards model to adjust for all 11 of the covariates (including coma incidence and administration of sedative and analgesic medications), delirium was associated with a more than 3-times higher risk of dying by 6 months (Table 3). In an additional analysis (data not shown), time-dependent cumulative doses of sedatives and narcotics were incorporated into the model, with similar results compared with the primary analysis. No collinearity was identified among the covariates used in these analyses (all variance inflation factors were ≤2, well below the threshold of 10 used to indicate potential collinearity). To complement the mortality analysis presented in Table 3, a similar analysis that considered the duration of delirium found that after adjusting for the covariates, each additional day an ICU patient spent in delirium was associated with a 10% increased risk of death (HR, 1.1; 95% confidence interval [CI], 1.0-1.3; $P=.03$).

Hospital Lengths of Stay. Compared with patients in the no delirium group, those who did develop delirium spent a median of 10 days longer in the hospital overall (Table 3). FIGURE 4A shows Kaplan-Meier curves of the probability of remaining in the hospital according to the clinical distinction of no delirium vs delirium. Figure 4B shows the no delirium and delirium groups further categorized by coma status, as in Figure 3B. At any given time during the hospital stay, patients diagnosed with delirium had an adjusted risk of remaining in the hospital that was twice as high as those who never developed delirium and a 60% greater risk of remaining in the wards after ICU discharge (Table 3). In a separate analysis, time-dependent cumulative doses of sedatives and nar-

Table 1. Baseline Characteristics of the Patients*

Characteristic	No. (%)† No Delirium (n = 41)	Delirium (n = 183)
Age, mean (SD), y	54 (17)	56 (17)
Men	18 (44)	95 (52)
Race		
White	32 (78)	145 (79)
Black	9 (22)	38 (21)
Charlson Comorbidity Index, mean (SD)	3.2 (2.8)	3.2 (2.8)
Vision deficits, No./total (%)‡	23/33 (70)	104/153 (68)
Hearing deficits, No./total (%)‡	5/32 (16)	29/152 (19)
mBDRS score, mean (SD)	0.14 (0.6)	0.23 (0.8)
Activities of daily living, mean (SD)	0.81 (2.4)	0.91 (2.3)
APACHE II score, mean (SD)	23.2 (9.6)	25.6 (8.1)
SOFA score, mean (SD)	9.5 (2.9)	9.6 (3.4)
ICU admission diagnosis§		
Sepsis and/or acute respiratory distress syndrome	24 (59)	78 (43)
Pneumonia	6 (15)	35 (19)
Myocardial infarction/congestive heart failure	4 (10)	15 (8)
Hepatic or renal failure	0	11 (6)
Chronic obstructive pulmonary disease	2 (5)	18 (10)
Gastrointestinal bleeding	2 (5)	18 (10)
Malignancy	0	7 (4)
Drug overdose	3 (7)	8 (4)
Other	14 (34)	53 (29)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; mBDRS, modified Blessed Dementia Rating Scale; SOFA, Sequential Organ Failure Assessment.
*All comparisons between the no delirium and delirium groups were nonsignificant ($P>.05$). See "Methods" section for descriptions of scales and for scale ranges.
†Except where noted otherwise.
‡Denominators indicate number of patients with available information.
§Recorded by the patients' medical team as the diagnoses most representative of the reason for admission to the ICU. Patients were sometimes given more than 1 admission diagnosis by the medical team, resulting in column totals >100%.

Table 2. Daily and Cumulative Doses of Sedative and Analgesic Medications

Drug	Daily ICU Dose, Mean (SD), mg: No Delirium (n = 41)	Delirium (n = 183)	P Value†	Cumulative ICU Dose, Mean (SD), mg*: No Delirium (n = 41)	Delirium (n = 183)	P Value†
Lorazepam	1.12 (2.2)	4.8 (12.8)	.01	9.0 (20.0)	49.2 (131.3)	.001
Propofol	36.6 (258.6)	48.4 (172.9)	.19	362.1 (1265.4)	591.2 (3942.2)	.20
Morphine	5.8 (17.0)	17.3 (163.8)	.79	48.0 (147.0)	168.1 (1321.9)	.66
Fentanyl	0.53 (1.7)	0.78 (1.7)	.22	3.1 (10.3)‡	8.7 (22.9)‡	.12

Abbreviation: ICU, intensive care unit.
*In the persistently comatose patients, the mean (SD) cumulative doses of these medications were: lorazepam, 15 (27) mg; propofol, 318 (1434) mg; morphine, 107 (345) mg; and fentanyl, 3 (12) mg.
†By Wilcoxon rank sum test for no delirium vs delirium.
‡Fentanyl is commonly reported to be 100 times more potent than morphine.[54] Therefore, using a dose conversion factor of 0.01, the median cumulative "morphine equivalent" dose of fentanyl given to patients in the no delirium and delirium groups would equate to 310 mg and 870 mg, respectively. While this mathematical conversion may be flawed or confounded in vivo, such large values are plausible considering fentanyl's initially short duration of action,[18] the potential for rapid tolerance to fentanyl,[62-64] and the administration of fentanyl as a continuous infusion rather than an intermittent bolus.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

cotics were incorporated into the model with similar results (data not shown) compared with the primary analysis. To complement the length-of-stay analyses presented in Table 3, similar analyses that considered the duration of delirium found that after adjusting for the covariates, each additional day spent in delirium by an ICU patient was associated with a 20% and a 10% increased risk of remaining in the hospital or in the wards, respectively (hospital length of stay: adjusted HR, 1.2; 95% CI, 1.1-1.3; $P=.002$; post-ICU length of stay: adjusted HR, 1.1; 95% CI, 1.0-1.2; $P=.04$).

Secondary Outcomes. Secondary outcomes included ventilator-free days in the ICU and neurologic impairment at discharge. There were significantly fewer days alive and free of the ventilator among patients in the delirium group (median, 19; IQR, 4-23) vs those in the no delirium group (median, 24; IQR, 19-26) ($P<.001$). After adjusting for the 11 covariates, this difference remained significant ($P=.03$). Cognitive assessments were not available at the time of hospital discharge for 51 of 179 survivors, due either to inability to complete testing or to unexpected discharge. One hundred twenty-eight survivors were tested, of whom 63 (49.2%) had discharge cognitive impairment as defined in the "Methods" section. Of those tested, twice as many patients in the delirium group vs the no delirium group exhibited cognitive impairment at hospital discharge (54.9% [56/102] vs 26.9% [7/26], respectively; $P=.01$), and multivariable analysis revealed that the patients in the delirium group were 9 times more likely to be discharged with cognitive impairment than were those in the no delirium group (adjusted HR, 9.1; 95% CI, 2.3-35.3; $P=.002$).

Table 3. Delirium Status and Clinical Outcomes Including 6-Month Mortality and Lengths of Stay

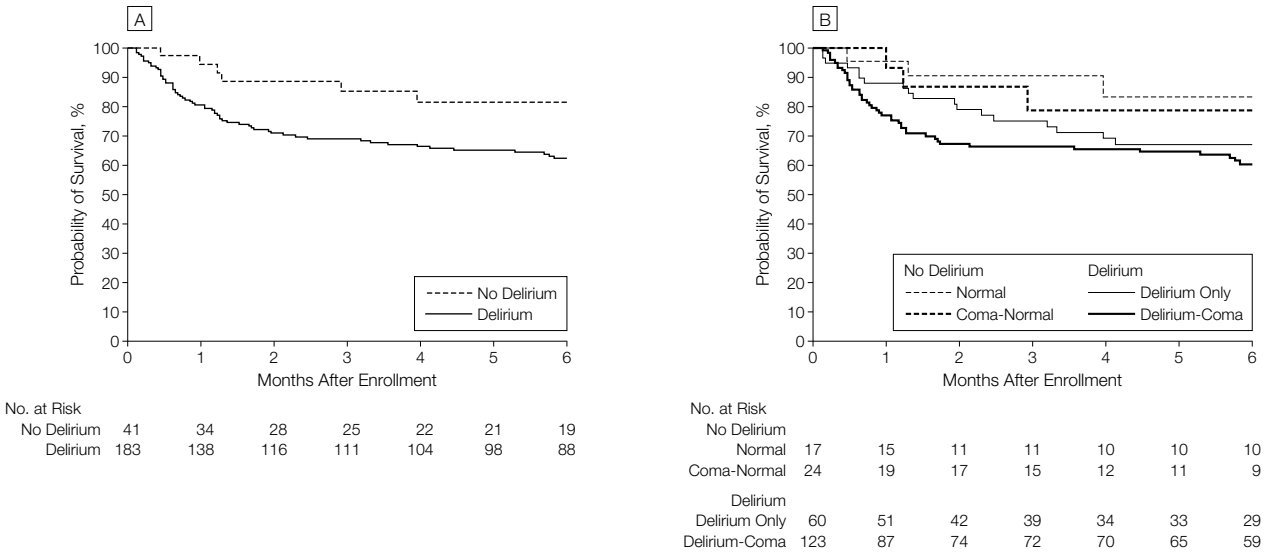
	No Delirium	Delirium	Adjusted *P* Value
6-Month Mortality			
No.	41	183	
Rate, No. (%)	6 (15)	63 (34)	
Adjusted HR (95% CI)*	Reference	3.2 (1.4-7.7)	.008
Hospital Stay			
No.	41	183	
Median (IQR), d	11 (7-14)	21 (19-25)	
Adjusted HR (95% CI)*	Reference	2.0 (1.4-3.0)	<.001
Post-ICU Stay†			
No.	40	156	
Median (IQR), d	5 (2-7)	7 (4-15.5)	
Adjusted HR (95% CI)*	Reference	1.6 (1.1-2.3)	.009

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range.
*Multivariable model incorporating baseline covariates including patient age at enrollment, Charlson Comorbidity Index,[43] modified Blessed Dementia Rating Scale score,[45] Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[7] Sequential Organ Failure Assessment (SOFA) score,[59,60] admitting diagnoses of sepsis or acute respiratory distress syndrome, and time-varying covariates for coma and use (yes/no) of lorazepam, propofol, morphine, and fentanyl. Assumptions of proportional hazard for the final models were evaluated by examining interactions between time and each variable in the model. Interaction terms were included in the model whenever nonproportionality of hazards was observed. For analysis of hospital length of stay, interactions were detected between time and APACHE II scores, SOFA scores, presence of coma, and use of lorazepam. No other significant interactions were observed.
†Twenty-eight patients died in the ICU (1 in the no delirium group and 27 in the delirium group, $P = .03$) and were therefore not included in the post-ICU length-of-stay analysis.

COMMENT

The development of delirium in these mechanically ventilated patients was associated with a 3-fold increase in risk of death after controlling for preexisting comorbidities, severity of illness, coma, and the use of sedative and analgesic medi-

Figure 3. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and 6-Month Survival



©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

cations. While development of coma is well recognized as a risk factor for death,[7,8,10,11] this investigation is the first to document a strong relationship between delirium and clinical outcomes after adjusting for coma. These data showed not only that ever developing this type of organ dysfunction was a predictor of death by 6 months after ICU discharge, but also that the number of days spent in a delirious state predicted mortality. In addition, delirium was not simply a transition state from coma to normal, as delirium occurred just as often among those who never developed coma as it did among those who did develop coma at some stage, and persisted in 11% of patients at the time of hospital discharge.

Monitoring for Delirium in the ICU

In the absence of data linking delirium to outcomes, few ICUs routinely monitor for delirium. Monitoring for delirium with the CAM-ICU, which is easily incorporated by nurses into their daily work and takes only 1 to 2 minutes, could allow the medical team to consider causes and modifications in their treatment of the patient experiencing this organ dysfunction[65,66] (downloadable materials and discussion available at http://www.icudelirium.org). We have found during a year-long implementation study incorporating more than 22000 patient observations that nursing staff readily incorporated such measurements into routine care,[67] in keeping with recently issued guidelines of the Society of Critical Care Medicine.[18]

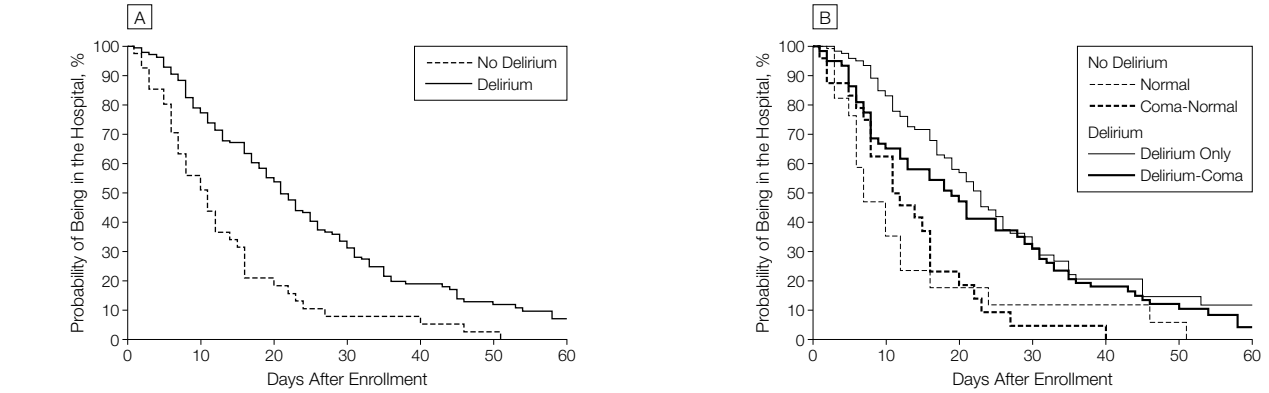
Perhaps the greatest benefit of incorporating delirium monitoring would be the enhanced detection of the hypoactive delirium subtype, often called "quiet" delirium because it is characterized by a flat affect or apathy and often present in otherwise calm and seemingly alert patients.[68] This is in contrast to the readily detected hyperactive delirium that is characterized by agitation, restlessness, attempting to remove catheters or tubes, hitting, biting, and emotional lability.[68] In this study, hypoactive delirium was present in over 50% of patients with normal or near-normal arousal. This type of brain dysfunction may portend a worse prognosis than hyperactive delirium, accounts for the majority of delirium observations, and is the most commonly missed subtype of delirium.[21,47,68-70]

Potentially Modifiable Risk Factors

Our findings suggest that an important opportunity for improving the care of critically ill patients may be the determination of modifiable risk factors for delirium in the ICU. Numerous risk factors for delirium have been identified, including preexisting cognitive impairment; advanced age; use of psychoactive drugs; mechanical ventilation; untreated pain; and a variety of medical conditions such as heart failure, prolonged immobilization, abnormal blood pressure, anemia, sleep deprivation, and sepsis.[17,34,71-81]

Some of the most readily implemented opportunities for improving care could be to correct brain ischemia/hypoxemia,[82] to modify the administration of psychoactive medications,[78] and to aggressively treat both underlying infection and the manifestations of severe sepsis, especially in elderly patients.[11,17,83-86] Regarding hypoxemia, Hopkins et al[82] found in 55 mechanically ventilated patients with acute lung injury that mean oxygen saturations were below 90% for 122 hours and below 85% for 13 hours per patient. Regarding use of psychoactive drugs, recent studies[87-89] have shown that reducing unnecessary use of sedatives and analgesics may improve patients' outcomes. Another approach to intervention would be to treat delirious patients with procognitive medications such as haloperidol, as recommended

Figure 4. Kaplan-Meier Analysis of Delirium in the Intensive Care Unit and Hospital Length of Stay



No. at Risk							
No Delirium	41	23	8	3	3	1	0
Delirium	183	137	82	43	20	13	4

No. at Risk							
No Delirium							
Normal	17	8	3	2	2	1	0
Coma-Normal	24	15	5	1	1	0	0
Delirium							
Delirium Only	60	38	25	17	8	5	2
Delirium-Coma	123	99	57	26	12	8	2

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

by the Society of Critical Care Medicine guidelines.[18] However, such interventions need to be tested in future research. Our multivariable analysis did demonstrate that delirium influenced outcomes even after adjusting for these medications.[89] Thus, the development of delirium was of clinical relevance above and beyond that attributed to iatrogenic administration of sedative and analgesic medications.

Long-term Cognitive Impairment

At the time of hospital discharge, there was substantial cognitive impairment in 1 out of every 2 survivors tested, which was significantly more common among patients who ever developed delirium compared with those who did not. An important limitation regarding this observation is that the patients were not tested for the presence of preexisting (ie, prior to ICU admission) cognitive impairment (a problem not easily resolved due to the emergent nature of these patients' illnesses). However, we did use a well-validated surrogate assessment of dementia to estimate and adjust for this possible confounder.

While long-term neuropsychological impairment following mechanical ventilation is now recognized with increasing frequency,[42,82] its relationship with delirium during ICU stay is not known and deserves further study. Ongoing delirium has been observed by others, including Levkoff et al,[32] who found that the majority of hospitalized elderly patients did not experience complete resolution of delirium symptoms prior to discharge. More recently, McNicoll and colleagues[90] reported that 40% of older ICU patients had ongoing delirium during the post-ICU period, and Kiely et al[91] found that almost 20% of elderly patients had delirium at the time of admission to postacute facilities.

Limitations and Future Directions

Four limitations of this study should be noted. The first limitation has to do with the delirium coding and the fact that study protocol mandated only once-daily CAM-ICU assessments. Assessing patients more often with the CAM-ICU will help to improve our understanding of the phenomenology of delirium in these patients. In the year-long implementation study mentioned above,[67] nurses adopted delirium monitoring so readily that they assessed patients more often than the twice-daily requirement. Our coding of patients as having or not having delirium for a given day has to do with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* definition of this disorder. However, it is important to remember that delirium, by definition, fluctuates over time. Due to the fluctuating nature of this disorder, it is considered present until cleared for 24 hours. It would be feasible to code the patients in 12-hour intervals. Even using such a schema, the delirium "episode" will be considered as ongoing until there are 2 consecutive 12-hour shifts with negative CAM-ICU assessments. Second, we did not examine the impact from the broad range of psychoactive medications other than sedatives and analgesics, patients' pharmacological interindividual variability in transport and metabolism of medications, or genetic predisposition to this form of brain injury. Third, while our cohort did incorporate a broad range of diagnoses in the medical ICU population, other types of critically ill patients should be investigated, including patients in trauma and surgical ICUs as well as those with baseline neurologic comorbidities.

Lastly, this observational study was not designed to prove a cause-and-effect relationship between delirium and clinical outcomes. However, there are data to support a pathophysiologic rationale for the brain as a potentiator (rather than merely a marker) of total-body injury during critical illness. The brain responds to systemic infections and injury with an inflammatory response of its own that also includes the production of cytokines, cell infiltration, and tissue damage.[92,93] Reports also indicate that local inflammation in the brain and subsequent activation of the central nervous system's immune responses are accompanied by peripheral manifestations of systemic inflammation, including production of large amounts of peripherally produced tumor necrosis factor α, interleukin 1, and interferon δ.[92,94-96] Such centrally mediated inflammation could influence the development or resolution of multiple organ dysfunction syndrome. Direct injury to the central nervous system induced by intracerebral endotoxin has also been shown to result in loss of the liver's ability to metabolize drugs independent of intraperitoneally administered endotoxin.[97-99] Thus, the brain produces its own signaling that likely influences the overall outcome of the patient. The exact nature of the signaling between the brain and other systemic organs remains to be elucidated. In the meantime, this study has demonstrated an important clinical association as well as the need for further examination, including etiologic and interventional studies.

CONCLUSIONS

In this single-center observational study, we found that delirium among mechanically ventilated patients in the ICU was associated with higher 6-month mortality and longer lengths of stay even after adjusting for numerous covariates. This study raises the question of how diligently delirium should be monitored in acutely ill patients, especially considering that validated instruments can be implemented with a high degree of reproducibility and rates of compliance at the bedside by those routinely caring for patients in the ICU. Some recent systematic reviews of sedation practices and their consequences in the ICU have not mentioned delirium,[100,101] while others have suggested that missing delirium in acutely ill patients should be considered a medical error.[25] Future studies are needed to determine whether prevention or treatment of delirium would change clinical outcomes including mortality, length of stay, cost of care, and long-term neuropsychological outcomes among survivors of critical illness.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

Author Affiliations: Department of Medicine, Division of General Internal Medicine and Center for Health Services Research and the Veterans Affairs Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC) (Drs Ely, Shintani, Speroff, Gordon, Inouye, Dittus, and Ms Truman), Division of Allergy/Pulmonary/Critical Care Medicine (Drs Ely and Bernard, Ms Truman), Department of Biostatistics (Drs Shintani, Speroff, and Harrell), and Department of Psychiatry (Dr Gordon), Vanderbilt University School of Medicine, Nashville, Tenn; and Department of Medicine, Yale University School of Medicine, New Haven, Conn (Dr Inouye)

Author Contributions: Drs Ely, Shintani, Speroff, and Dittus and Ms Truman had full access to the all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Ely, Shintani, Truman, Gordon, Bernard, Dittus.
Acquisition of data: Ely, Truman.
Analysis and interpretation of data: Ely, Shintani, Truman, Speroff, Gordon, Harrell, Inouye, Bernard, Dittus.
Drafting of the manuscript: Ely, Shintani, Truman.
Critical revision of the manuscript for important intellectual content: Ely, Truman, Speroff, Gordon, Harrell, Inouye, Bernard, Dittus.
Statistical expertise: Ely, Shintani, Speroff, Harrell, Dittus.
Obtained funding; study supervision: Ely, Bernard, Dittus.
Administrative, technical, or material support: Ely, Truman, Gordon, Inouye, Bernard, Dittus.

Funding/Support: Dr Ely is a recipient of the Paul Beeson Faculty Scholar Award from the Alliance for Aging Research and of a K23 from the National Institutes of Health (AG01023-01A1) and the Veterans Affairs Tennessee Valley Geriatric Research, Education, and Clinical Center. Dr Inouye is a recipient of a Midcareer Award (K24AG00949) from the National Institute on Aging and a Donaghue Investigator Award (DF98-105) from the Patrick and Catherine Weldon Donaghue Medical Research Foundation.
Role of the Sponsor: The Alliance for Aging Research, National Institutes of Health, National Institute on Aging, and the Patrick and Catherine Weldon Donaghue Medical Research Foundation had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.
Acknowledgment: We thank all of the dedicated and open-minded ICU staff and Meredith Gambrell, who contributed to this work. In addition, we thank Geeta Mehta, MD; Derek Angus, MB, MPH; Craig Weinert, MD, MPH; and Jean-Louis Vincent, MD, PhD, who provided important early feedback on the manuscript.

REFERENCES

1. Schmitz R, Lantin M, White A. *Future Needs in Pulmonary and Critical Care Medicine*. Cambridge, Mass: Abt Associates; 1998.
2. Angus DC, Linde-Zwirble WT, Clermonte G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
3. Luhr OR, Karlsson M, Thorsteinsson A, Rylander C, Frostell CG. The impact of respiratory variables on mortality in non-ARDS and ARDS patients requiring mechanical ventilation. *Intensive Care Med*. 2000; 26:508-517.
4. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1985; 132:485-489.
5. Ely EW, Wheeler AP, Thompson BT, Ancuklewicz M, Steinberg KP, Bernard GR. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. *Ann Intern Med*. 2002;136:25-36.
6. Esteban A, Anzueto A, Alia I, et al. Indications for, complications from, and outcome of mechanical ventilation: effect of age. *Am J Respir Crit Care Med*. 2000; 161:A385.
7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-829.
8. Ferreira FL, Peres Bota D, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286: 1754-1758.
9. Young GB, Bolton CF, Archibald YM, Austin TW, Wells GA. The electroencephalogram in sepsis-associated encephalopathy. *J Clin Neurophysiol*. 1992; 9:145-152.
10. Sprung CL, Peduzzi PN, Shatney CH, et al. The impact of encephalopathy on mortality in the sepsis syndrome: the Veterans Administration Systematic Sepsis Cooperative Study Group. *Crit Care Med*. 1990; 18:801-806.
11. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy: definitions, etiologies, and mortalities. *JAMA*. 1996;275: 470-473.
12. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. *Crit Care Med*. 2000;28:3019-3024.
13. Bleck TP, Smith MC, Pierre-Louis SJ, Jares JJ, Murray J, Hansen CA. Neurologic complications of critical medical illnesses. *Crit Care Med*. 1993;21:98-103.
14. Ely EW, Siegel MD, Inouye S. Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med*. 2001; 22:115-126.
15. McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med*. 2000;160:906-909.
16. Geary SM. Intensive care unit psychosis revisited: understanding and managing delirium in the critical care setting. *Crit Care Nurs Q*. 1994;17:51-63.
17. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340: 669-676.
18. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002; 30:119-141.
19. Ely EW, Stephens RK, Jackson JC, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. *Crit Care Med*. 2004;32:106-112.
20. Lipowski ZJ. Delirium in the elderly patient. *N Engl J Med*. 1989;320:578-582.
21. Meagher DJ, Hanlon DO, Mahony EO, Casey PR, Trzepacz PT. Relationship between symptoms and motoric subtype of delirium. *J Neuropsychiatry Clin Neurosci*. 2000;12:51-56.
22. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med*. 1994;97:278-288.
23. Gustafson Y, Brannstorm B, Norberg G, et al. Underdiagnosis and poor documentation of acute confusional states in elderly hip fracture patients. *J Am Geriatr Soc*. 1991;39:760-765.
24. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM. Nurses' recognition of delirium and its symptoms. *Arch Intern Med*. 2001;161:2467-2473.
25. Sanders AB. Missed delirium in older emergency department patients: a quality-of-care problem. *Ann Emerg Med*. 2002;39:338-341.
26. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horowitz RI. Clarifying confusion: the confusion assessment method. *Ann Intern Med*. 1990;113: 941-948.
27. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age Ageing*. 1999;28:551-556.
28. Rabins PV, Folstein MF. Delirium and dementia: diagnostic criteria and fatality rates. *Br J Psychiatry*. 1982;140:149-153.
29. Inouye SK, Schlesinger MJ, Lyndon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med*. 1999;106:565-573.
30. Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc*. 1992;40:601-606.
31. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002;162:457-463.
32. Levkoff SE, Evans DA, Liptzin B, et al. Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med*. 1992; 152:334-340.
33. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med*. 2000;160:786-794.
34. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271:134-139.
35. Riker R, Picard JT, Fraser G. Prospective evaluation of the sedation-agitation scale for adult critically ill patients. *Crit Care Med*. 1999;27:1325-1329.
36. Sessler CN, Gosnell M, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. *Am J Respir Crit Care Med*. 2002;166:1338-1344.
37. 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;289:2983-2991.
38. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001;27:859-864.
39. 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;286:2703-2710.
40. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med*. 2001;29:1370-1379.
41. 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;27:1892-1900.
42. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med*. 2003;31:1226-1234.
43. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
44. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:94-99.
45. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.
46. Wijdicks EFM. *Neurologic Complications of Critical Illness*. New York, NY: Oxford University Press; 2002.
47. Meagher DJ. Delirium: optimising management. *BMJ*. 2001;322:144-149.
48. American Psychiatric Association. *Diagnostic and*

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015

Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:123-133.
49. Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med*. 2002; 30:1772-1777.
50. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
51. O'Connor DW, Pollitt PA, Hyde JB, et al. The reliability and validity of the Mini-Mental State in a British community survey. *J Psychiatr Res*. 1989;23:87-96.
52. Lorentz WJ, Scanlan JM, Boorson S. Brief screening tests for dementia. *Can J Psychiatry*. 2002;47: 723-733.
53. Tangalos EG, Smith GE, Ivnik RJ, et al. The Mini-Mental State Examination in general medical practice: clinical utility and acceptance. *Mayo Clin Proc*. 1996;71:829-837.
54. Cammarano WB, Drasner K, Katz J. Pain control, sedation, and use of muscle relaxants. In: Hall JB, Schmidt GA, Wood LD, eds. *Principles of Critical Care Medicine*. New York, NY: McGraw-Hill Publishers; 1998:90-97.
55. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J Biometrics*. 1972;26:579-581.
56. Cox DR. Regression models and life-tables. *J R Stat Soc*. 1972;34:187-220.
57. Crowley J, Hu M. Covariance analysis of heart transplant survival data. *J Am Stat Assoc*. 1977;72: 27-36.
58. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer-Verlag; 2000.
59. Vincent JL, Moreno R, Takala J, et al, for the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-Related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22:707-710.
60. Vincent JL, Mendonca Ad, Cantraine F, et al, Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med*. 1998;26: 1793-1800.
61. Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression Analysis and Other Multivariable Methods*. Belmont, Calif: Duxbury Press; 1988:210-211.
62. Trujillo KA, Akil H. Opiate tolerance and dependence: recent findings and synthesis. *New Biol*. 1991; 3:915-923.
63. Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. *Anesth Analg*. 1998;86:1307-1311.
64. Eilers H, Philip LA, Bickler PE, McKay WR, Schumacher MA. The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesth Analg*. 2001;93:213-214.
65. American Psychiatric Association. Practice guidelines for the treatment of patients with delirium. *Am J Psychiatry*. 1999;156(suppl):1-20.
66. American Psychiatric Association. What is Delirium? Available at: http://www.psych.org/psych_pract/treatg/patientfam_guide/Delirium.pdf. Accessed March 9, 2004.
67. Truman B, Shintani A, Jackson J, Peterson JF, Thomason J, Ely EW. Implementation of the SCCM guidelines for sedation and delirium monitoring in the ICU. *Am J Respir Crit Care Med*. 2003;167:A969.
68. Truman B, Ely EW. Monitoring delirium in critically ill patients. *Crit Care Nurse*. 2003;23:25-36.
69. Camus V, Burtin B, Simeone I, Schwed P, Gonthier R, Dubos G. Factor analysis supports the evidence of existing hyperactive and hypoactive subtypes of delirium. *Int J Geriatr Psychiatry*. 2000;15: 313-316.
70. Peterson JF, Truman BL, Shintani A, Thomason JWW, Jackson JC, Ely EW. The prevalence of hypoactive, hyperactive, and mixed-type delirium in medical ICU patients. *J Am Geriatr Soc*. 2003;51:S174.
71. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;275:852-857.
72. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272:1518-1522.
73. Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med*. 1998;13:204-212.
74. Litaker D, Locala J, Franco K, Bronson DL, Tannous Z. Preoperative risk factors for postoperative delirium. *Gen Hosp Psychiatry*. 2001;23:84-89.
75. Rahkonen T, Eloniemi-Sulkava U, Halonen P, et al. Delirium in the non-demented oldest old in the general population: risk factors and prognosis. *Int J Geriatr Psychiatry*. 2001;16:415-421.
76. Rolfson DB, McElhaney JE, Rockwood K, et al. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can J Cardiol*. 1999;15:771-776.
77. Schor JD, Levkoff SE, Lipsitz LA, et al. Risk factors for delirium in hospitalized elderly. *JAMA*. 1992; 267:827-831.
78. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med*. 2001;27:1297-1304.
79. Aldemir M, Ozen S, Kara IH, Sir A, Bac B. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care*. 2001;5:265-270.
80. Granberg A, Malmros CW, Bergbom IL, Lundberg D. Intensive care unit syndrome/delirium is associated with anemia, drug therapy and duration of ventilation treatment. *Acta Anaesthesiol Scand*. 2002; 46:726-731.
81. Morrrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci*. 2003;58:76-81.
82. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;160:50-56.
83. Ely EW, Angus DC, Williams MD, Bates B, Qualy R, Bernard GR. Drotrecogin alfa (activated) treatment of older patients with severe sepsis. *Clin Infect Dis*. 2003;37:187-195.
84. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein c for severe sepsis. *N Engl J Med*. 2001;344:699-709.
85. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.
86. Vincent JL, Abraham E, Annane D, Bernard G, Rivers E, Van Den Berghe G. Reducing mortality in sepsis: new directions. *Crit Care*. 2002;6:S1-S18.
87. Kollef MH, Levy NT, Ahrens T, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest*. 1999;114:541-548.
88. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999; 27:2609-2615.
89. 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;342:1471-1477.
90. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc*. 2003;51:591-598.
91. Kiely DK, Bergmann MA, Murphy KM, Jones RN, Orav EJ, Marcantonio ER. Delirium among newly admitted postacute facility patients: prevalence, symptoms, and severity. *J Gerontol A Biol Sci Med Sci*. 2003; 58:M441-M445.
92. Perry VH, Andersson B, Gordon S. Macrophages and inflammation in the central nervous system. *Trends Neurosci*. 1993;16:268-273.
93. Rothwell NJ, Luheshi G, Toulmond S. Cytokines and their receptors in the central nervous system: physiology, pharmacology and pathology. *Pharmacol Ther*. 1996;69:85-95.
94. Woiciechowsky C, Asudullah K, Nestler D, et al. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. *Nat Med*. 1998;4:808-813.
95. Woiciechowsky C, Schoening B, Daberkow N, et al. Brain IL-1 beta induces local inflammation but systemic anti-inflammatory response through stimulation of both hypothalamic-pituitary-adrenal axis and sympathetic nervous system. *Brain Res*. 1999;816: 563-571.
96. Nicholson TE, Renton KW. The role of cytokines in the depression of CYP1A activity using cultured astrocytes as an in vitro model of inflammation in the CNS. *Drug Metab Dispos*. 2002;30:42-46.
97. Renton KW, Nicholson TE. Hepatic and central nervous system cytochrome P450 are down-regulated during lipopolysaccharide-evoked localized inflammation in brain. *J Pharmacol Exp Ther*. 2000; 294:524-530.
98. Shimamoto Y, Kitamura H, Hoshi H, et al. Differential alterations in levels of hepatic microsomal cytochrome P450 isozymes following intracerebroventricular injection of bacterial lipopolysaccharide in rats. *Arch Toxicol*. 1998;72:492-498.
99. Shimamoto Y, Kitamura H, Iwai M, Saito M, Kazusaka A, Fujita S. Mechanism of decrease in levels of hepatic P450 isozymes induced by intracerebral endotoxin: independence from sympathetic nervous and adrenocortical systems. *Arch Toxicol*. 1999;73:41-49.
100. Ostermann ME, Keenan SP, Seiferling RA, Sibbald W. Sedation in the intensive care unit. *JAMA*. 2000;283:1451-1459.
101. Shapiro BA, Warren J, Egol A, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med*. 1995;23:1596-1600.

 ©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Universite Laval User on 05/11/2015