Intensive Care Med (2001) 27: 1892–1900
DOI 10.1007/s00134-001-1132-2

ORIGINAL

The impact of delirium in the intensive care unit on hospital length of stay

E. W. Ely
S. Gautam
R. Margolin
J. Francis
L. May
T. Speroff
B. Truman
R. Dittus
G. R. Bernard
S. K. Inouye

Received: 10 April 2001
Final revision received: 10 April 2001
Accepted: 14 September 2001
Published online: 8 November 2001

Grant support: Dr. Ely is a recipient of the AFAR Pharmacology in Aging Grant, and is a Beeson Scholar as well as a Geriatric Research and Education Clinical Center (GRECC) investigator. Dr. Inouye is a recipient of a research grant (#RO1AG12551) and 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

E. W. Ely (✉)
Divisions of Allergy/Pulmonary/
Critical Care Medicine,
Center for Health Services Research,
Vanderbilt University Medical Center,
6th Floor Medical Center East, Nashville,
TN 37232–8300, USA
E-mail: wes.ely@mcmail.vanderbilt.edu
Phone: +1-615-936 2795
Fax: +1-615-936 1269

E. W. Ely · S. Gautam · L. May · T. Speroff · B. Truman · R. Dittus · G. R. Bernard
Departments of Internal Medicine,
Divisions of General Internal Medicine
and Center for Health Services Research,
Vanderbilt University Medical Center,
Nashville, Tenn., USA

R. Margolin
Department of Geriatric Psychiatry and
Neuroscience, Vanderbilt University
Medical Center, Nashville, Tenn., USA

J. Francis
Division of Quality and Data Management,
St. Vincent Hospital Health System,
Indianapolis, Ind., USA

S. K. Inouye
Department of Internal Medicine,
Division of Geriatrics, Yale University
Medical Center, New Haven, Conn., USA

Abstract *Study objective*: To determine the relationship between delirium in the intensive care unit (ICU) and outcomes including length of stay in the hospital.
Design: A prospective cohort study.
Setting: The adult medical ICU of a tertiary care, university-based medical center.
Participants: The study population consisted of 48 patients admitted to the ICU, 24 of whom received mechanical ventilation.
Measurements: All patients were evaluated for the development and persistence of delirium on a daily basis by a geriatric or psychiatric specialist with expertise in delirium assessment using the Diagnostic Statistical Manual IV (DSM-IV) criteria of the American Psychiatric Association, the reference standard for delirium ratings. Primary outcomes measured were length of stay in the ICU and hospital.
Results: The mean onset of delirium was 2.6 days (S. D. ± 1.7), and the mean duration was 3.4 ± 1.9 days. Of the 48 patients, 39 (81.3 %) developed delirium, and of these 29 (60.4 %) developed the complication while still in the ICU. The duration of delirium was associated with length of stay in the ICU ($r = 0.65$, $P = 0.0001$) and in the hospital ($r = 0.68$, $P < 0.0001$). Using multivariate analysis, delirium was the strongest predictor of length of stay in the hospital ($P = 0.006$) even after adjusting for severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration.
Conclusions: In this patient cohort, the majority of patients developed delirium in the ICU, and delirium was the strongest independent determinant of length of stay in the hospital. Further study and monitoring of delirium in the ICU and the risk factors for its development are warranted.

Keywords Delirium · Aging · Geriatrics · Cognitive impairment · Encephalopathy · Mechanical ventilation · Sedatives · Analgesics · Protocol · Respiratory diseases · Critical care

Abbreviations *APACHE* Acute Physiology and Chronic Health Evaluation · *DSM* Diagnostic Statistical Manual (of American Psychiatric Association) · *ICU* Intensive Care Unit · *mBDRS* modified Blessed Dementia Rating Scale · *MMSE* Mini-Mental State Examination

Introduction

Patients in the intensive care unit (ICU) are at very high risk for the development of delirium due to factors such as multi-system illnesses and comorbidities, the use of psychoactive medications, and age. Among general medical or surgical patients, the frequency of delirium varies from 15% to 50% [1, 2, 3]. These demographic data reflect non-ICU patients and there are, unfortunately, sparse data concerning the demographics of delirium in the ICU [4, 5] and even less on its impact on outcomes among medical ICU patients. The incidence of acute respiratory failure requiring mechanical ventilation rises tenfold from the age of 55–85 years [6], resulting in greater numbers of elderly patients treated in our ICUs [7, 8]. Without appropriate preventive and management strategies, the aging of the population will likely result in an increased burden of delirium among mechanically ventilated patients across the country [9, 10, 11], a factor which could strongly effect discharge rates to nursing homes following hospital discharge [2, 12].

While recent studies have selected delirium and pharmacologic issues (which are inter-related) as two of the top three most important target areas for quality of care improvement in vulnerable older adults [13], nearly all delirium investigations have excluded medical ICU patients who are often receiving prolonged sedation on mechanical ventilators [1, 2, 14, 15, 16, 17]. Likewise, recent systematic reviews and clinical practice guidelines of sedation practices and consequences in the ICU have not even mentioned delirium [18, 19, 20].

As the medical community strives to advance many facets of care for both younger and older patients treated in the ICU, it is imperative that we improve our understanding of the frequency and duration of delirium on outcomes in the ICU. In this investigation of medical ICU patients, we assessed for the development of delirium in the ICU and the presence of persistent cognitive deficits at the time of hospital discharge. The main goal of this study was to determine the impact of delirium on commonly monitored clinical outcomes such as length of stay in the ICU and in the hospital.

Methods

Patients

The study population included both ventilated and non-ventilated adult medical ICU patients admitted to the Vanderbilt University Medical Center. Fifty-three consecutive patients were enrolled into the study out of the 68 patients admitted to the ICU during the study period. Exclusion criteria defined a priori included a history of chronic dementia, psychosis, mental retardation, or other neurologic diseases that would confound the diagnosis of delirium (e.g., cerebrovascular accident with residual cognitive impairment), and patient or family refusal to participate. Twelve patients were excluded due to underlying chronic dementia or psychosis, and there were three refusals, leaving the 53 patients who were enrolled. Five patients were never evaluated by the reference standard geriatric or psychiatric specialist and were therefore excluded from further analysis. This left 48 patients upon which to base the current report.

Study protocol

The institutional review board approved this study, and informed consent was obtained from the patient and/or the surrogate. Two study nurses enrolled patients each morning and recorded baseline demographics, severity of illness data using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [21], activities of daily living [22], and risk factors for delirium derived from data in the literature [2, 3, 14, 15, 23, 24, 25, 26, 27]. The modified Blessed Dementia Rating Scale (mBDRS) [28] was used to screen for dementia via family or surrogate interviews. This use of the mBDRS is consistent with its original intent, as it was validated as a dementia screening instrument by comparing the structured mBDRS surrogate interview with the patients' neuropathologic findings at autopsy. The surrogates also completed a set of global questions (rated on a 1–5 scale) that were related to their perceptions of the presence or absence of dementia and the likelihood of the development of delirium. While no patients with documented chronic dementia were enrolled in this investigation, it is possible that patients with mild dementia were admitted to the ICU without a prior diagnosis. To account for the possibility of such baseline cognitive deficits, we defined a priori a subgroup of patients as having "possible mild dementia" at enrollment if any of the following three criteria were met: (1) the geriatric psychiatric expert rated them as demented; (2) they had an mBDRS [28] of 3 or greater (lower than the usual cutoff of 4 or greater, thereby increasing sensitivity for detection of dementia); or (3) a rating on the question answered by the surrogate of 3 or greater out of 5 as "possibly having dementia."

Once enrolled, patients were followed daily until hospital discharge (see Reference Standard evaluations below). At the time of hospital discharge, the patients completed the Folstein Mini-Mental State Examination (MMSE) [29], Geriatric Depression Scale [30], SF-12 [31], and Maugeri Respiratory Foundation-28 (MRF-28) [32] quality of life instruments. The SF-12 is summarized using mental and physical component scores, which range from 0 to 100 (100 = optimal). The MRF–28 is a disease-specific quality of life instrument designed for use in patients with chronic respiratory diseases [32], and it is scored from 0 to 100 with lower numbers indicating better quality of life (0 = optimal) based on respiratory disability.

Reference standard delirium evaluations

All cognitive assessments were conducted in the afternoon between 2 p.m and 5 p.m. The geriatric or psychiatric experts served as the reference standard by completing the DSM IV [33] criteria for delirium (see Appendix) or a rating for a more severely impaired sensorium such as stupor or coma. These latter states were defined as follows: (1) *stupor* – difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; and (2) *coma* – unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so

that the interview is difficult or impossible even with maximal prodding.

Our two experts (one a geriatrician with extensive experience in delirium assessment [2, 27, 34, 35, 36] and the other a geriatric psychiatrist with 25 years of experience on a busy in-hospital consult liaison service) performed independent patient evaluations. They were allowed the flexibility of utilizing any and all means of patient evaluation, testing, and data gathering (i.e., chart review, lab data, and nursing notes), thus maximizing their ability to arrive at a reference standard rating of cognitive functioning. This included speaking with family members, the patient's bedside clinical nurse (as opposed to study nurse), and any others who observed the patient's behavior and thinking that day. The delivery of psychoactive medications (e.g., sedatives and analgesics) was not interrupted or modified for the purposes of the delirium assessments, but was left strictly in the hands of the managing clinicians who were not co-investigators. The managing clinicians and the treatment team were blinded to the reference standard evaluations.

Statistical analysis

For multiple linear regression analysis, the independent or explanatory variable was the duration of delirium in days that had begun in the ICU (i.e., "ICU-onset" delirium). The dependent or response variables chosen for the multiple regression analysis were length of stay in ICU, length of stay in hospital, Folstein MMSE score, depression as measured by the GDS, and quality of life as measured by SF12 and MRF-28 forms. Covariates used in the analysis included age, gender, APACHE II, and number of days of psychoactive drug use. For this investigation, *psychoactive drug days* were counted as any day on which a patient received either a narcotic or a benzodiazepine either IV or PO (recognizing, of course, that numerous other drugs are implicated to have deliriogenic features). Days were rounded to the nearest digit. Since the histogram of hospital stay showed a skewed distribution, the data were transformed using the log scale. The transformed variable was approximately normally distributed. The correlation of each of the outcome variable (e.g., ICU length of stay and hospital length of stay) was calculated with each of the covariates in univariate analysis. The relationship between delirium and outcome adjusted for covariates was examined using multiple linear regression analysis. Statistical significance was defined as a P value < 0.05. Severity of illness was described using the APACHE II score [21]. Statistical analysis was performed using SAS Version 6 (SAS Institute, Cary, N.C., USA).

Results

Demographics characteristics

The reference standard geriatric or psychiatric experts evaluated a total of 48 patients in this investigation. The mean age of the population was 58 ± 19 (mean ± S.D.), and 26 (54 %) were mechanically ventilated on enrollment (Table 1). The distribution by race was 82 % Caucasian, 17 % African-American, and 1 % Hispanic. Severity of illness as measured by APACHE II was a mean of 18.7 ± 7.8. The mBDRS mean score was 0.78 ± 0.13, well below the level of 4 typically used to predict the presence of baseline dementia. Using a liberal definition of "possible mild dementia" as defined in Methods, there were only 11 (22 %) patients with this condition. Patients had a variety of admission diagnoses as outlined in Table 1.

Table 1 Patient characteristics

Characteristics	Frequency (total $n = 48$)
Age (mean ± S.D.)	58 ± 19.4
Male	28 (58 %)
Race	
Caucasian	82 %
African-American	17 %
Hispanic	1 %
APACHE II Score (mean ± S.D.)[a]	18.7 ± 7.8
Mechanical ventilation	26 (54 %)
Blessed Dementia Rating Scale[b]	0.78 ± 1.13
Possible mild dementia[c]	11 (22 %)
ICU Admission diagnosis	*n* (%)
Acute Respiratory Distress Syndrome	14 (29 %)
Myocardial infarction or arrhythmia	7 (15 %)
Congestive heart failure	7 (15 %)
Hepatic or renal failure	6 (13 %)
Chronic Obstructive Pulmonary Disease	4 (8 %)
Gastrointestinal bleeding	3 (6 %)
Malignancy	4 (8 %)
Drug overdose	3 (6 %)

[a] APACHE II denotes Acute Physiology and Chronic Health Evaluation II score [21], an assessment of severity of illness
[b] The modified Blessed Dementia Rating Scale is an instrument to measure a patient's baseline likelihood of dementia using surrogate interviews, scores of 4 or greater indicate likely dementia [28].
[c] Patients were defined as having "possible mild dementia" at enrollment if any of the following three criteria were met: (1) the geriatric or psychiatric expert rated them as demented; (2) they had a mBDRS [28] of 3 or greater (lower than the usual cutoff of 4 or greater, thereby increasing sensitivity for detection of dementia; or (3) a rating by the surrogate of 3 or greater out of 5 as "possibly having dementia"

Risk factors for delirium

The prevalence of each risk factor in the population is presented in Table 2. The mean number of identified risk factors for delirium in these patients was 11 ± 4, with a range of 3–17 risk factors present. The most frequent risk factor present in this cohort was the use of benzodiazepines or narcotics in 47 of 48 patients (98 %), although the dose and frequency of administration were not recorded for this study.

Table 2 Prevalence of risk factors for delirium in ICU cohort. The list of risk factors for delirium was derived from the literature using the references listed below. Visual or hearing impairments were determined by patient or family report and by subjective (not formal) evaluation. Malnutrition was recorded if patient had a low prealbumin, cholesterol below 100 mg/dl, or received no feeds for > 48 h in the hospital. Sleep disturbances are an obvious risk factor, but this was not objectively tracked for this study [2, 3, 14, 15, 23, 24, 25, 26, 27]

Risk factor	Frequency, *n* (%)
Administration of benzodiazepines or narcotics	47 (98%)
Rectal or bladder (Foley) catheters	38 (79%)
Visual or hearing impairment[a]	33 (69%)
Central venous catheters	32 (67%)
Hypo or hyperglycemia (< 80 or > 120 mg/dl)	25 (52%)
Hypo or hypernatremia (< 135 or > 145 mg/dl)	24 (50%)
Hypothermia or fever (< 36 ° or > 38 °C)	21 (44%)
Use of physical restraints or posey vest	21 (44%)
Age over 70 years	17 (35%)
Tube feeding or total parenteral nutrition	15 (31%)
Prior history of depression	14 (29%)
Cardiogenic or septic shock	14 (29%)
BUN/Creatinine ratio ≥18	13 (27%)
Renal failure (creatinine > 2.0 mg/dl)	10 (21%)
History of congestive heart failure	9 (19%)
History of stroke, epilepsy	5 (10%)
Drug overdose or illicit drug use within week	5 (10%)
Transfer from a nursing home	4 (8%)
Alcohol abuse within a month	3 (6%)
Malnutrition[b]	3 (6%)
Liver disease (bilirubin > 2.0 mg/dl)	2 (4%)
Hypo- or hyperthyroidism	1 (2%)
Human immunodeficiency virus infection	1 (0%)

[a] Baseline vision or hearing deficits were recorded if patients wore corrective lenses (glasses, bifocals, or contacts) or had a hearing aid, respectively, as well as if the family reported that the patient had any documented impairment in vision or hearing

[b] Malnutrition was recorded if the patient was below 80% of predicted ideal body weight or if the person had baseline hypoalbuminemia < 2.5 mg/dl

Table 3 Patient outcomes in entire cohort. Data are presented as mean ± S.D unless otherwise noted. Outcomes instruments were completed at the time of hospital discharge. The Folstein mini mental state examination yields a score from 0 to 30, with a score of < 24 generally used to indicate significantly depressed cognitive abilities [29]. The geriatric depression scale yields a score from 0 to 30, with a score of 11 or higher indicates possible depression with 84% sensitivity and 95% specificity [30]. The Short Form-12 is a generic quality of life instrument that is widely used and scored according to a mental and physical component score, each with a range of values from 0 to 100 (100 = optimal) [31]. The Maugeri respiratory foundation-28 is a disease-specific quality-of-life instrument designed for use in patients with chronic respiratory diseases [32], and it is scored from 0 to 100 with lower numbers indicating better quality of life (0 = optimal) based on respiratory disability

Selected outcomes	Entire cohort (*n* = 48)
Survival to hospital discharge	42 (87.5%)
Days on ventilator (*n* = 26)	3.5 ± 3.4
Days in ICU	4.2 ± 2.9
Days in hospital	7.3 ± 7.2
Delirium in the Intensive Care Unit, *n* (%)	29 (60.4%)
Delirium in the hospital, *n* (%)	39 (81.3%)
Duration of delirium in days	3.4 ± 1.9
Folstein Mini Mental State Score	22.8 ± 6.1
Geriatric Depression Scale	13.1 ± 7.8
Quality-of-life data at hospital discharge	
Short Form-12 (generic)	
Mental Component Score	48.5± 15.0
Physical Component Score	34.0 ± 9.3
Magueri Respiratory-28 (disease-specific)	22.9 ± 27.1

Clinical outcomes

Survival and length of stay data are presented in Table 3 along with other selected outcomes. Over 80% (*n* = 39) of patients developed delirium during their hospital stay, with the majority of cases (29 of 39, or 74% of all delirium) occurring initially in the ICU with an average time of onset between the second and third day. Five patients (10%) remained comatose throughout the study and were not classified as delirious. The mean duration of delirium was 3.4 ± 1.9 days, with a range of 1–8 days. In this investigation, there were 131 patient days in which active delirium was present (excluding comatose days), and a simultaneously performed rating by the geriatric or psychiatric expert revealed that this delirium was "hypoactive or quiet" delirium in 123 (94%) of cases and hyperactive or agitated delirium in eight (6%) of cases.

Over one-fourth of the survivors (11 of 42, 26%) were delirious within 24 h of hospital discharge. Of 42 patients surviving to hospital discharge, 31 completed the discharge evaluation that included the Folstein MMSE, depression scale, and quality-of-life evaluations. Although application of sensitive baseline criteria identified only 11 (22%) with possible dementia at entry, 18 of 31 (58%) patients had MMSE scores below 24 at hospital discharge (< 24 is the standard cut-off to indicate significant deficits by MMSE). Of these 18, 13 (72.2%) were not delirious at discharge. Of the 11 judged "possibly mildly demented" at baseline, only two had MMSE on discharge below 24, leaving 16 cognitively impaired patients who had no baseline indication of dementia. The mean Geriatric Depression Scale score of 13.1 ± 7.8 was above the usual cutoff to indicate depression, and 15 of 31 (48%) patients had scores of 11 or higher. The quality-of-life instruments used (SF-12 and MRF-28) are summarized in Table 3. The four cognitive questions included in the MRF-28 revealed that 13 of 31 (42%) patients evaluated at hospital discharge

Table 4 Simple linear regression (univariate) analysis: predictors of lengths of stay in ICU and hospital

Variable	ICU Length of stay		Length of hospital stay	
	Correlation coefficient	*P* Value	Correlation coefficient	*P* Value
Duration of delirium[a]	0.65	0.0001	0.68	< 0.0001
APACHE II[b]	0.07	0.66	0.22	0.15
Age	0.26	0.15	0.01	0.94
Gender	0.15	0.42	0.27	0.09
Drug days[c]	0.56	0.0007	0.67	< 0.0001

[a] Delirium with onset in the ICU (i.e., "ICU-onset" delirium), duration measured in days
[b] APACHE II = denotes Acute Physiology and Chronic Health Evaluation II score [21]
[c] Drug days = number of days that a patient received psychoactive medications including either narcotics or benzodiazepines

Table 5 Multiple linear regression model: predictors of lengths of stay in ICU and hospita*

Variable[a]	ICU Length of stay (days)			Length of hospital stay (days)		
	Beta	95 % C.I.	*P* Value	Beta	95 % C.I.	*P* Value
Intercept	1.21	–	–	1.82	–	–
Duration of delirium [#]	1.09	0.95–1.26	0.09	1.18	1.05–1.32	0.006
APACHE II	0.99	0.96–1.02	0.69	1.01	0.98–1.03	0.61
Age	1.00	0.99–1.02	0.25	1.00	0.99–1.00	0.38
Gender	0.95	0.57–1.56	0.82	1.22	0.84–1.75	0.30
Drug days	1.18	1.02–1.34	0.03	1.13	1.01–1.26	0.04

[a]Dependent variables were log transformed prior to analysis, but estimates have been back transformed into original scale for presentation. Beta coefficients can be interpreted as average stay in days (intercept) or expected difference in stay between patients with and without the listed condition. 95 % C.I. = 95 % confidence intervals, APACHE II = denotes Acute Physiology and Chronic Health Evaluation II score [21], drug days = number of days that a patient received psychoactive medications designated in Methods
[b]Delirium with onset in the ICU (i.e., "ICU-onset" delirium), duration measured in days. The adjusted r^2 for delirium in relation to the ICU stay was 0.37, and for the hospital stay the adjusted r^2 was 0.55

were having trouble with at least three of the following: forgetting names more than before, feeling absent minded, forgetting what they were going to say, or having difficulty maintaining concentration even on topics interesting to them.

Simple and multiple linear regression analysis

Simple linear regression (univariate analysis) showed that both ICU stay and hospital stay were significantly correlated with duration of delirium and psychoactive drug days, while APACHE II score, age, and gender were not (Table 4). The duration of delirium with onset in the ICU was associated with length of stay in the ICU ($r = 0.65$, $P = 0.0001$) and in the hospital ($r = 0.68$, $P < 0.0001$). The duration of delirium also correlated with the duration of benzodiazepine or narcotic use ($r = 0.54$, $P = 0.0005$), but less well with APACHE II ($r = 0.37$, $P = 0.02$) and age ($r = 0.27$, $P = 0.09$). The development of delirium was poorly correlated with other outcomes including Folstein MMSE ($r = –0.14$, $P = 0.47$), SF-12 ($r = –0.30$, $P = 0.27$), and MRF-28 ($r = 0.10$, $P = 0.65$). The results of the multiple linear regression analysis are displayed in Table 5. Using multiple regression analysis, delirium with onset in the ICU was the strongest predictor of length of stay in the hospital ($P = 0.006$) even after adjusting for severity of illness, age, gender, race, and days of psychoactive drug utilization. The model's adjusted r^2 for delirium in relation to the length of ICU stay was 0.37, and for the length of hospital stay the adjusted r^2 was 0.55.

Discussion

Delirium complicates the hospital stay of more than 2–3 million elderly patients per year in the U.S., involving over 17.5 million in-patient days and accounting for at least $4 billion in Medicare expenditures [1, 2, 3, 10, 23, 37]. Medical ICU patients are among the sickest patients in our entire health care system and consume substantial resources with median costs of $25,000 to $30,000 per patient [38], and costs per quality adjusted life-year ranging from $29,000 to $110,000 depending upon prognostic strata [39]. It is not known whether delirium contributes independently to poor outcomes. We have conducted a delirium investigation in the ICU us-

ing reference standard evaluators and found that delirium occurred in 80 % of all patients and was the strongest predictor of length of stay in the hospital even after adjusting for severity of illness and other covariates. The prevalence of delirium in this investigation was four times higher than the control rate of delirium a recently reported cohort of medical patients [1].

The fact that delirium was an independent determinant of length of stay sends an important message to the ICU community that this poorly monitored yet extremely common complication of ICU stay should achieve a high priority for future study. In the ICU setting, as in terminal cancer patients [40], it will be important to determine if delirium is merely a marker of illness and physical frailty, an avoidable iatrogenic complication, or an independent contributor to poor neurological outcomes and survival. The development of delirium in non-ICU patients has an associated in-hospital mortality of 25–33 % [3, 12, 41, 42]. Francis and Kapoor [34] found that 2-year mortality in patients having experienced delirium was 39 % versus 23 % in controls. In addition, a 3-site epidemiological delirium study showed that delirium was an important independent predictor of the combined outcome of death or nursing home placement [41].

In this investigation, we found that ICU patients had an inordinately high number of risk factors to develop delirium. While benzodiazepines and narcotics were the most prevalent risk factor in this cohort (administered to 98 % of patients), numerous other risk factors must be considered, as we found that their use explained only 29 % (i.e., $r^2 = 0.29$) of the variation in duration of delirium. In fact, the mean number of risk factors per patient was 11. Clinical prediction rules have repeatedly shown that it is possible to stratify patients into risk groups depending upon the number of risk factors present [2, 14, 25, 43]. Patients with three or more of these risk factors have been considered "high risk" for delirium [2, 14, 40, 43], and in ICU patients, this magnitude of risk is nearly universal. In practical terms, the risk factors for delirium can be divided into three categories [2, 3, 14, 15, 23, 24, 25, 26, 27]: 1) the acute illness itself; 2) host factors including age or chronic health problems; and 3) iatrogenic or environmental factors. Modifications of risk factors in the ICU such as the use of psychoactive drugs, maintenance of sleep/wake cycles, attempts at prevention of malnutrition, optimization of the use of restraints, and adjustments in care to account for visual or hearing impairment could help improve the incidence and/or duration of delirium [1].

This observational investigation did not address treatment of delirium, but we believe that two important concepts warrant mentioning: 1) in delirious patients, a search for all reversible precipitants is the first line of action; and 2) symptomatic treatments should be considered when available and not contraindicated (e.g., haloperidol). In two important and recently reported clinical trials, dose reductions of narcotics and benzodiazepines have been shown to improve outcomes in the ICU for mechanically ventilated patients [44, 45], but the effects on delirium or long-term cognitive impairment were not measured.

A major limitation of our ability to determine the best therapy for delirium has been that standard delirium assessment instruments [16, 46, 47] were not validated for use in intubated, non-verbal patients. Prior to routine monitoring of delirium in the ICU population, better instruments need to be developed for nurses or other ICU personnel to measure delirium as an outcome for investigations and quality assurance [11, 48].

Delirium remains unrecognized by the clinician in as many as 66–84 % of patients experiencing this complication [2, 17], and it may be attributed incorrectly to dementia, depression, or just an "expected" occurrence in the critically ill, elderly patients [2]. In addition, the term "delirium" has not been used to categorize the types and degrees of cognitive impairment found in septic patients in the ICU, with the default, all-inclusive term of "septic encephalopathy" (encompassing delirium, stupor, and coma) being used instead [49, 50, 51, 52].

It is important for the medical community (especially those who care for critically ill patients in the ICU) not only to distinguish delirium from other degrees of cognitive impairment, but also to recognize that subtypes of delirium exist. These subtypes of delirium are classified by psychomotor activity as either hypoactive, hyperactive, or mixed [53, 54]. When patients are allowed to emerge from the effects of sedation, they may do so peacefully or in a combative manner. On one extreme are the "peaceful" patients, who are often assumed erroneously to be thinking clearly. These patients with hypoactive or quiet delirium represented 94 % of all episodes of delirium in our investigation. This subtype is manifested as decreased mental activity and inattention, and is frequently overlooked by physicians and nurses [12, 27, 35]. Many clinicians expect delirium to present with agitation or hallucinations, features that are not required for the diagnosis. Failing to recognize deficits in cognitive function places these fragile patients at risk for aspiration and reintubation [55, 56, 57]. When patients are in a combative state, they are usually referred to as having "intensive care syndrome" or "ICU psychosis," which is the hyperactive subtype of delirium [4, 5, 53, 58]. These terms may be a potentially dangerous misnomer, because they imply that increased psychomotor activity and hallucinations are an expected outcome in the ICU [4, 5, 26, 53, 58, 59]. In this cohort, hyperactive delirium was present in only 6 % of the episodes of delirium.

This investigation has several limitations. Most importantly, the size and the duration of follow-up should

be extended in future cohorts to better determine the role of delirium on mortality. In addition, future studies of larger cohorts including more elderly ICU patients with diverse causes of respiratory failure should assess neuropsychological function beyond the ICU stay in order to determine the prevalence of and risk factors for persistent deficits. Recent data on long-term outcomes after the acute respiratory distress syndrome (ARDS) demonstrated impaired neuropsychological function in 78% of patients at one-year follow-up [60]. We did not find an association between delirium and impaired quality of life in our study, yet this may represent another limitation of either the size of the study or the quality of life instruments chosen. For example, the MRF-28 has not been used previously in an ICU cohort (it was chosen because it has both disease-specific questions for respiratory patients as well as those related to cognitive impairment). Recently, data has begun to emerge regarding quality of life measures following ICU care [61, 62, 63], including the role of sedatives and neuromuscular blocking agents in psychiatric disorders after ICU care [64], but no data are available for delirium. Our risk factor analysis, while thorough in comparison to previous ICU delirium studies, lacked sleep monitoring and employed simple methods to track psychoactive drug use. Future studies should track both of these risk factors in a more detail. While this investigation did not find a striking correlation between age and delirium, the cohort contained a relatively young population and the study was not powered to evaluate this relationship. Lastly, sepsis itself should be tracked as an independent risk factor for delirium in ICU cohorts, considering the aforementioned entity of septic "encephalopathy," which often includes delirium.

In conclusion, we have shown that delirium developing in the ICU was a strong predictor of length of stay in the hospital. This investigation should raise awareness of delirium as a complication of stay in the ICU for critically ill patients. This complication may be modifiable and deserves further study. Monitoring delirium in the ICU in patients receiving mechanical ventilation may be a future priority in the ICU, especially as the age of ICU patients continues to increase, thereby introducing older patients who are vulnerable to this complication.

Appendix

DSM IV Criteria for delirium

Reference standard evaluations were performed by the Geriatric or Psychiatric experts using all available information including patient examinations and interactions, nurse and family interviews, physicians' and nurses' notes, laboratory values, and any other chart data present.

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by one of the following:
   i. The direct physiological consequences of a general medical condition.
   ii. The direct result of medication use or substance intoxication (Substance Intoxication Delirium).
   iii. The direct result of a withdrawal syndrome (Substance Withdrawal Delirium).
   iv. The direct result of more than one of the above etiologies (Delirium Due to Multiple Etiologies).

The diagnosis of cognitive impairment involves careful observations of the abilities of the patient and knowledge of the patient's former level of functioning. In order to identify all cases cognitive impairment, we have adopted the following measures: 1) the above DSM criteria and mental status definitions will be consistently employed; 2) a geriatric psychiatrist's evaluation will be conducted to determine which of these criteria are met by the patient. This will involve a bedside evaluation and screening for cognitive and attention deficits; 3) lastly, interviewing the family and nurse who provide the majority of patient care will establish baseline functioning and identify fluctuations [33].

References

1. Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM (1999) A multicomponent intervention to prevent delirium in hospitalized older patients. New Engl J Med 340: 669–676
2. Francis J, Martin D, Kapoor WN (1990) A prospective study of delirium in hospitalized elderly. JAMA 263: 1097–1101
3. Levkoff SE, Evans DA, Liptzin B, Clearly PD, Lipsitz LA, Wetle TT, Reilly CH, Pilgrim DM, Schor J, Rowe J (1992) Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med 152: 334–340

4. Granberg A, Engberg B, Lundberg D (1996) Intensive care syndrome. Intensive Crit Care Nurs 12: 173–182
5. Geary SM (1994) Intensive care unit psychosis revisited: understanding and managing delirium in the critical care setting. Crit Care Nurs 17: 51–63
6. Behrendt CE (2000) Acute respiratory failure in the United States: incidence and 31-day survival. Chest 118: 1100–1105
7. Jakob SM, Rothen HU (1997) Intensive care 1980–1995: change in patient characteristics, nursing workload and outcome. Intensive Care Med 23: 1165–1170
8. Chelluri L, Grenvik A, Silverstein M (1995) Intensive care for critically ill elderly: mortality, costs, and quality of life. Review of the literature. Arch Intern Med 155: 1013–1022
9. Ely EW, Evans GW, Haponik EF (1999) Mechanical ventilation in a cohort of elderly patients admitted to an intensive care unit. Ann Intern Med 131: 96–104
10. O'Keeffe S, Lavan J (1997) The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 45: 174–178
11. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard G, Inouye S (2001) Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). Crit Care Med 29: 1370–1379
12. Inouye SK, Schlesinger MJ, Lyndon TJ (1999) Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. Am J Med 565–573
13. Sloss EM, Solomon DH, Shekelle PG, Young RT, Saliba D, MacLean CH, Rubenstein LZ, Schnelle JF, Kamberg CJ, Wenger NS (2000) Selecting target conditions for quality of care improvement in vulnerable older adults. J Am Geriatr Soc 48: 363–369
14. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, Donaldson MC, Whittemore AD, Sugarbaker DJ, Poss R, Haas S, Cook F, Orav J, Lee TH (1994) A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 271: 134–139
15. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, Katz N, Cook F, Orav J, Lee TH (1994) The relationship of postoperative delirium with psychoactive medications. JAMA 272: 1518–1522
16. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horowitz RI (1990) Clarifying confusion: the confusion assessment method. Ann Intern Med 113: 941–948
17. Inouye SK (1994) The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med 97: 278–288
18. Ostermann ME, Keenan SP, Seiferling RA, Sibbald W (2000) Sedation in the intensive care unit. JAMA 283: 1451–1459
19. Young C, Knudsen N, Hilton A, Reves JG (2000) Sedation in the intensive care unit. Crit Care Med 28: 854–866
20. Shapiro BA, Warren J, Egol A, Greenbaum D, Jacobi J, Nasraway S, Schein R, Spevetz A, Stone J (1995) Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Crit Care Med 23: 1596–1600
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13: 818–829
22. Katz S, Ford AB, Moskowitz RW, Jackson BAJMW (1963) Studies of illness in the aged- the index of ADL: a standardized measure of biological and psychosocial function. JAMA 185: 94–99
23. Williams-Russo P, Urquhart BL, Sharrock NE, Charlson ME (1992) Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 40: 759–767
24. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER (1998) The impact of postoperative pain on the development of postoperative delirium. Anesth Anal 86: 781–785
25. Inouye SK, Viscoli C, Horwitz RI, Hurst LD, Tinetti ME (1993) A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 119: 474–481
26. Wilson LM (1972) Intensive care delirium; the effect of outside deprivation in a windowless unit. Arch Intern Med 130: 22–23
27. Francis J, Kapoor WN (1990) Delirium in hospitalized elderly. J Gen Intern Med :65–79
28. Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Brit J Psychiatry 114: 797–811
29. Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198
30. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED (1997) Screening for depression in elderly primary care patients. Arch Intern Med 157: 449–454
31. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M (1998) Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the international quality of life assessment project. J Clin Epidemiol 51: 1171–1178
32. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW (1999) Analysis of factors that characterise health impairment in patients with chronic respiratory failure. Eur Respir J 13: 1293–1300
33. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, D. C., USA, pp 123–133
34. Francis J, Kapoor WN (1992) Prognosis after hospital discharge of older medical patients with delirium. J Am Geriatr Soc 40: 601–606
35. Francis J (1992) Delirium in older patients. J Am Geriatr Soc 40: 829–838
36. Francis J (1996) Drug-induced delirium. CNS Drugs 5: 103–114
37. Statistical abstract of the United States (1996) Bureau of the Census, Washington, D. C., USA
38. Ely EW, Baker AM, Evans GW, Haponik EF (2000) The cost of respiratory care in mechanically ventilated patients with chronic obstructive pulmonary disease. Crit Care Med 28: 408–413
39. Hamel MB, Phillips RS, Davis RB, Teno J, Connors AF, Desbiens N, Lynn J, Dawson NV, Fulkerson W, Tsevat J (2000) Outcomes and cost-effectiveness of ventilator support and aggressive care for patients with acute respiratory failure due to pneumonia or acute respiratory distress syndrome. Am J Med 109: 614–620
40. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, Bruera ED (2000) Occurrence, causes, and outcome of delirium in patients with advanced cancer. Arch Intern Med 160: 786–794
41. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P (1998) Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 13: 234–242

42. American Psychiatric Association (1999) Practice guideline for the treatment of patients with delirium. Am J Psychiatry 156: 1–20
43. Inouye SK, Charpentier PA (1996) Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA 275: 852–857
44. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH (1999) Effect of a nursing implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 27: 2609–2615
45. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. New Engl J Med 342: 1471–1477
46. Trzepacz PT, Baker RW, Greenhouse J (1987) A symptom rating scale for delirium. Psychiatry Res 23: 89–97
47. Trzepacz PT, Dew MA (1995) Further analyses of the delirium rating scale. Gen Hosp Psychiatry 17: 75–79
48. Ely EW, Inouye S, Bernard G, Gordon S, Francis J, Margolin R, May L, Truman B, Speroff T, Gautam S, Dittus R (2001) Delirium in the mechanically ventilated patients: validity and reliability of the confusion assessment method for the ICU (CAM-ICU). Am J Respir Crit Care Med (in press)
49. Isensee LM, Weiner LJ, Hart BG (1989) Neurologic disorders in a medical intensive care unit. J Crit Care 4: 208–210
50. Bleck TP, Smith MC, Pierre-Louis SJ, Jares JJ, Murray J, Hansen CA (1993) Neurologic complications of critical medical illnesses. Crit Care Med 21: 98–103
51. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED (2000) Pathophysiology of septic encephalopathy: a review. Crit Care Med 28: 3019–3024
52. Eidelman LA, Putterman D, Putterman C, Sprung CL (1996) The spectrum of septic encephalopathy: definitions, etiologies, and mortalities. JAMA 275: 470–473
53. Meagher DJ, Hanlon DO, Mahony EO, Casey PR, Trzepacz PT (2000) Relationship between symptoms and motoric subtype of delirium. J Neuropsychiatry Clin Neurosci 12: 51–56
54. Liptzin B, Levkoff SE (1992) An empirical study of delirium subtypes. Br J Psychiatry 161: 843–845
55. Epstein SK, Ciubotaru RL, Wong JB (1997) Effect of failed extubation on the outcome of mechanical ventilation. Chest 112: 186–192
56. Epstein SK, Ciubotaru RL (1998) Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. Am J Respir Crit Care Med 158: 489–493
57. Vallverdu I, Calaf N, Subirana M, Net A, Benito S, Mancebo J (1999) Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial of patients weaning from mechanical ventilation. Am J Respir Crit Care Med 158: 1855–1862
58. McGuire BE, Basten CJ, Ryan CJ, Gallagher J (2000) Intensive care unit syndrome: a dangerous misnomer. Arch Intern Med 160: 906–909
59. Justic M (2000) Does "ICU psychosis" really exist? Crit Care Nurs 20: 28–37
60. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V (1999) Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 160: 50–56
61. Montuclard L, Garrouste-Orgeas M, Timsit JF, Misset B, Jonghe BD, Carlet J (2000) Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. Crit Care Med 28: 3389–3395
62. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA (2000) Long-term health related quality of lifein survivors of sepsis. Short form 36: a valid and reliable measure of health-related quality of life. Crit Care Med 28: 3599–3605
63. Orlando R, III (2000) Quality of life in intensive care unit survivors: a place for outcomes research in critical care. Crit Care Med 28: 3755–3756
64. Nelson BJ, Weinert CR, Bury CL, Marinelli WA, Gross CR (2000) Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med 28: 3626–3630