Published in final edited form as:
*Crit Care Med*. 2014 June ; 42(6): 1480–1486. doi:10.1097/CCM.0000000000000247.

# Corticosteroids and transition to delirium in patients with acute lung injury

**Matthew P Schreiber, MD, MHS**[1], **Elizabeth Colantuoni, PhD**[2,3], **Oscar J Bienvenu, MD, PhD**[3,7], **Karin J Neufeld, MD, MPH**[3,7], **Kuan-Fu Chen, MD, PhD**[8], **Carl Shanholtz, MD**[9], **Pedro A Mendez-Tellez, MD**[3,5], and **Dale M Needham, MD, PhD**[3,4,6]

[1]Division of Pulmonary and Critical Care, University of Nevada School of Medicine, Las Vegas, NV

[2]Department of Biostatistics, Johns Hopkins University, Baltimore, MD

[3]Outcomes after Critical Illness and Surgery (OACIS) Group, Johns Hopkins University, Baltimore, MD

[4]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD

[5]Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University, Baltimore, MD

[6]Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD

[7]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD

[8]Chang Gung University and Chang Gung Memorial Hospital at Keelung, Taiwan

[9]Division of Pulmonary and Critical Care Medicine, University of Maryland, Baltimore, MD

## Abstract

**Objective—**Delirium is common in mechanically ventilated patients in the intensive care unit (ICU) and associated with short- and long-term morbidity and mortality. The use of systemic corticosteroids is also common in the ICU. Outside of the ICU setting, corticosteroids are a recognized risk factor for delirium, but their relationship with delirium in critically ill patients has not been fully evaluated. We hypothesized that systemic corticosteroid administration would be associated with a transition to delirium in mechanically ventilated patients with acute lung injury (ALI).

**Design—**Prospective cohort study

**Setting—**Thirteen ICUs in 4 hospitals in Baltimore, MD

**Patients—**520 mechanically ventilated adult patients with ALI

**Measurements and Main Results—**Delirium evaluation was performed by trained research staff using the validated CAM-ICU screening tool. A total of 330 (64%) of the 520 patients had at least two consecutive ICU days of observation in which delirium was assessable (e.g., patient was

Address for Correspondence: Dale M. Needham, MD, PhD 1830 E. Monument Street, 5th floor Baltimore, MD 21205 dale.needham@jhmi.edu Ph: 410-955-3467 Fax: 410-955-0036.

non-comatose), with a total of 2286 days of observation and a median (inter-quartile range [IQR]) of 15 (9, 28) observation days per patient. These 330 patients had 99 transitions into delirium from a prior non-delirious, non-comatose state. The probability of transitioning into delirium on any given day was 14%. Using multivariable Markov models with robust variance estimates, the following factors (adjusted odds ratio, 95% confidence interval) were independently associated with transition to delirium: older age (compared to <40 years old, 40-60 years (1.81, 1.26 to 2.62) and >=60 years (2.52, 1.65 to 3.87)) and administration of any systemic corticosteroid in the prior 24 hours (1.52, 1.05 to 2.21).

**Conclusions—**After adjusting for other risk factors, systemic corticosteroid administration is significantly associated with transitioning to delirium from a non-delirious state. The risk of delirium should be considered when deciding about the use of systemic corticosteroids in critically ill patients with ALI.

### Keywords

Delirium; Steroids; Intensive Care; Markov Chains; Treatment Outcome; Acute Lung Injury

Delirium is common in mechanically ventilated patients in the intensive care unit (ICU) and associated with short- and long-term morbidity and mortality.[1-6] Delirium can be ameliorated through addressing modifiable risk factors, such as immobilization, the administration of benzodiazepines and opioids, and sleep disruption.[7-14] While delirium may involve neuroinflammation, systemic corticosteroids, despite their anti-inflammatory properties, are recognized as a risk factor for delirium and other psychiatric phenomena in hospitalized patients.[15-18] However, there has been little evaluation of the association between systemic corticosteroids and delirium in the ICU setting. Such investigation is important because corticosteroids are frequently used with evolving data regarding their potential benefits within the ICU setting.[19-24] Hence, further evaluation of the potential risks of corticosteroids[25] is warranted to assist with decision-making regarding the benefits and risks of their use.

Given their high severity of illness and frequent requirement for mechanical ventilation and sedation, patients with acute lung injury (ALI) are at especially high risk for delirium and also frequently receive corticosteroids.[14, 20, 21, 26-29] Hence, using a cohort of ALI patients, our objective was to evaluate if systemic corticosteroid use was an independent risk factor for transitioning to delirium from a noncomatose, non-delirious state.

## METHODS

### Patients

This project was conducted as a secondary analysis of a prospective cohort study (trial registration NCT00300248) of 520 consecutive, mechanically ventilated patients with ALI [30] recruited from 13 ICUs at four teaching hospitals in Baltimore, MD between October 2004 and October 2007. All study ICUs utilized goal directed sedation protocols and the two largest study sites utilized daily interruption of sedation infusions. Patients were excluded from the prospective cohort study if they met any of the following criteria: (1) preexisting comorbid illness with a life expectancy of six or less months (for example, metastatic

cancer), (2) preexisting cognitive impairment or communication/language barriers, (3) no fixed address, (4) transferred from another hospital and had pre-existing acute lung injury for >24 hours, (5) mechanically ventilated for >5 days before onset of acute lung injury, (6) previous lung resection, and (7) a physician order for no escalation of care in the ICU (for example, no vasopressors) at ALI onset.[31]

### Primary outcome: transition to delirium

The primary outcome was patients' transition from a "normal" state (i.e., non-delirious and noncomatose) to a delirious state on the next day, as described herein. Patients' sedation and delirium status was evaluated once-daily by rigorously trained research staff using the validated Richmond Agitation Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU), respectively.[32, 33] On the basis of these assessments, on a daily basis, patients are classified into 1 of 3 mutually exclusive categories: (1) comatose (RASS of −4 or −5), (2) delirious (RASS >-3 with a positive CAM-ICU), or (3) normal (RASS >-3 with a negative CAM-ICU); this information was used to determine the primary outcome

### Primary exposure: systemic corticosteroids

The primary exposure was receipt of systemic corticosteroids in the ICU, as obtained from medication administration records and modeled as daily administration status (yes/no) and total daily dose (in milligrams of prednisone-equivalents).[34]

### Covariates: potential confounders

Based on prior literature, [1, 10, 11, 35-40] a number of potential confounding variables were considered in this analysis. In addition to patient demographics (age, sex, and race), the following baseline variables were evaluated using data collected from review of medical records: Charlson comorbidity index[35], prior cerebral vascular accident, current or prior excess alcohol use, current or prior illicit drug use, and prior home use (either as-needed or routine scheduled dosing) of any medication within each of the following drug classes: systemic corticosteroids, opioids, or benzodiazepines. The following ICU covariates also were considered: type of ICU (medical vs. surgical), Acute Physiology and Chronic Health Evaluation II (APACHE II)[41] severity of illness score at ICU admission, daily Sequential Organ Failure Assessment (SOFA) score[42] (excluding the neurologic component to prevent adjusting for a component of the primary outcome within the regression model), any use of continuous dialysis, daily presence of sepsis (evaluated based on pre-existing diagnostic criteria[43] and microbiologically documented infection), and daily administration status (yes/no) and total daily dose of opioids or benzodiazepines (presented as morphine- and midazolam-equivalent doses, respectively).[44-46] Propofol and dexmedetomidine were rarely used in the study-site hospitals and therefore not relevant covariates for this analysis.

### Statistical Analysis

Descriptive statistics were calculated for continuous and categorical variables. To appropriately model continuous exposure variables (e.g. age), their individual associations

with the probability of transitioning to delirium was evaluated through inspection of locally weighted least squares (LOWESS) plots.[47]

A first-order Markov model[48] was used to estimate the relative odds of transitioning from a normal state to a delirious state on the next day. This model uses logistic regression analysis to evaluate the primary exposure variable (systemic corticosteroids) against delirium (vs. normal state) on a specific day, adjusted for: (1) the presence of delirium on the immediately prior day, and (2) the previously described covariates. Robust variance estimates were used to account for correlation in the repeated daily measures of delirium status within patients beyond the first-order Markov assumption.[49] As done in prior studies,[36, 50] any days in which delirium status was not assessable (e.g., due to coma, subject refusal, or a missed assessment) or in which delirium status was not available on the immediately prior day (e.g., day of admission, coma, subject refusal, or missed assessment) were not included in the analysis in order to restrict the analysis to consecutive days of completed delirium assessments.

Among all of the covariates considered for this analysis (as described previously), individual covariates were considered for inclusion in the multivariable regression model if they had an association, at $p \leq 0.2$, with the primary outcome variable based on bivariable logistic regression analyses. In the final multivariable regression model, the absence of multicolinearity was confirmed by evaluating variance inflation factors[49] and goodness-of-fit testing was confirmed with the Hosmer-Lemeshow statistic.[49] All statistical analyses were performed using Stata version 12 (Stata Corp., College Station, TX, USA). The study was approved by institutional review boards at all participating sites.

## Results

A total of 330 (64%) of the 520 consecutive, mechanically ventilated ALI patients had at least 2 consecutive days that were assessable for delirium, representing 2286 days of observation, with a median (inter-quartile range [IQR]) of 15 (1, 28) days of observation per patient. The 330 patients had a median (IQR) age of 51 (41, 63) years, with 55% male and 60% Caucasian (Table 1). Patients' median (IQR) APACHE II score was 24 (19, 30), with 70% of patients admitted to a medical ICU (MICU) (Table 1) and 37% of patients receiving systemic corticosteroids.

Delirium was documented on one or more days in 83% of patients with a median (IQR) duration of delirium of 7 (3, 12) days. Among 733 previous days with an observed normal state, there were 99 transitions to delirium (14% daily probability of transition). Corticosteroids were administered on the prior day in 41% and 34% of days with and without a transition to delirium, respectively (Table 2). Additionally, a transition to delirium was present in 16% and 12% of days with and without administration of corticosteroids respectively. Among days in which corticosteroids were received, the median (IQR) dose in those with and without a transition to delirium was 44 (13, 75) and 23 (13, 50) milligrams of prednisone-equivalent respectively.

Results of the bivariable and multivariable logistic regression models are presented in Table 3. In the multivariable model, the administration of systemic corticosteroids was significantly associated with transition to delirium (adjusted Odds Ratio [OR] = 1.52, 95% Confidence Interval [CI] = 1.05 - 2.21); however, in those receiving corticosteroids, there was no significant association between dose and delirium transition. Additionally, older age (compared to <40 years old, 40-60 years (adjusted OR: 1.81, 95% CI: 1.26 to 2.62) and >=60 years (2.52, 1.65 to 3.87)) was independently associated with delirium transition.

Because of a potential benefit from the anti-inflammatory effect of systemic corticosteroids on neuroinflammation associated with delirium, post-hoc sensitivity analyses were conducted to evaluate if early use of corticosteroids had a protective effect against transition to delirium. The following multivariable analyses demonstrated no association between early use of corticosteroids and transition to delirium: (1) evaluation of corticosteroids administered on ICU day 1 (p=0.63), (2) evaluation of corticosteroids administered on ICU day 1 or as an outpatient prior to admission (p=0.91), and (3) evaluation of corticosteroids administered on ICU day 1 only among those receiving steroids prior to admission (p=0.2). Furthermore, assessment of corticosteroid administration in terms of glucocorticoid-equivalents demonstrated no material difference from our primary multivariable results.

## Discussion

In this prospective, multi-site cohort study evaluating 330 ALI patients with 2286 ICU days of observation, there is a significantly independent association between systemic corticosteroid use and transition to delirium the following day. Older age was also independently associated with transition to delirium.

Systemic corticosteroids are frequently used in the ICU [19-24] with 37% of ALI patients in this cohort having received them. However, use of systemic corticosteroids in the ICU is variable with evolving evidence regarding their use in critically ill patients; [19-24] thus, motivating the need to better understand their potential risks and benefits in this setting.

Our findings are consistent with prior studies of corticosteroids and delirium conducted outside of the ICU setting. For example, Kenna et.al.[16] reported on a case series of 55 patients and describe a range of neuropsychiatric outcomes, including delirium, occurring after steroid administration. Furthermore, in a multicenter cohort study of patients receiving >20 mg/day of prednisone-equivalents, Fardet et.al.[51, 52] observed that 52.5% of patients developed neuropsychiatric complications including delirium. A retrospective analysis of primary care patients also reported an independent association between corticosteroid administration and delirium, confusion or disorientation (hazard ratio 5.14, 95% Confidence Interval 4.54 - 5.82). Additionally, in a trial specifically evaluating delirium in a mixed-setting postoperative population adjusted for use of ICU care, an association with systemic corticosteroids has been described.[53]

While our study reveals an important relationship between corticosteroid administration (as a binary variable) and transition to delirium, we could not detect a significant dose-relationship. Our study identified a wide range of corticosteroid doses. However, of the 898

days on which a corticosteroid was administered, 72% of these days were at or above the dosing threshold previously associated with neuropsychiatric complications [51, 52] and this may have precluded our identifying a dose-response relationship.

Compared to this prior research, our study has the advantage of prospectively evaluating, on a daily basis, transition to delirium, as evaluated by trained research staff using a validated screening instrument (CAM-ICU), and adjusting for potential confounding risk factors. Our study builds on prior assessments of delirium in mechanically ventilated patients in the ICU.[36, 54-57] Unlike prior ICU studies assessing systemic corticosteroids and delirium,[54, 58, 59] our analysis demonstrated a statistically significant independent relationship, likely attributable to greater sample size, more frequent corticosteroid administration, and patient population that was at high risk for delirium.

Several studies [36, 56, 60, 61] have demonstrated a significant association of benzodiazepines with transitioning to delirium. Our study also identified a positive relationship between benzodiazepine administration and transition to delirium, but this relationship was not statistically significant in our multivariable model, perhaps because we adjusted for covariates, such as daily SOFA score and corticosteroids, which were not always considered in prior studies.[36, 56, 60, 61] Others have also identified a positive, but not statistically significant, relationship of benzodiazepine and delirium, but did identify a significant association with coma.[62]

Our study also confirms age as an important predictor of transitioning to delirium.[36, 58, 59] Particularly in older patients, attention should be directed towards addressing modifiable risk factors for delirium (e.g., use of corticosteroids and immobilization [7-9]).

Our study has potential limitations. First, as an observational study, it cannot prove a cause-effect relationship between systemic corticosteroids and delirium, and residual confounding may contribute to our findings. However, a randomized trial designed to specifically address this relationship between corticosteroids and delirium is not ethically possible. Hence, we encourage investigators in all future randomized, placebo-controlled studies of corticosteroids to include a safety outcome related to daily delirium status as well as secondary outcomes related to long-term cognitive and psychiatric outcomes[5, 63] to more fully evaluate the potential neuropsychological risks and benefits of corticosteroids in the critically ill. Second, we were unable to evaluate all known risk factors for delirium. In particular, dementia could not be evaluated since it was an exclusion criterion for our study and data regarding restraint use was unavailable. However, the exclusion of dementia helped reduce potential measurement error in our primary outcome since delirium assessment in critically ill demented patients is challenging. Additionally, we were unable to evaluate the effects of propofol[64] and dexmedetomidine[60, 65] since they were rarely used in the study hospitals. Our study did not have the ability to adjust for the indication for usage of systemic corticosteroids, and as previously noted the percentage of patients (72%) receiving clinically important doses of corticosteroids may have precluded our ability to identify a dose-response. Furthermore, we were unable to assess the association between delirium and mortality as there were only 15 deaths in the entire study population in which delirium status was available on the previous day with none of these occurring on a day following a non-

comatose, non-delirious state (the structure of our Markov model). Finally, there may be limitations regarding the generalizability of our results because only ALI patients at teaching hospitals were studied with once daily assessments of delirium. However, because our patient population included a diverse range of patient demographics and comorbidities, both medical and surgical ICUs, and multiple hospitals, we believe our study is a valuable contribution to prior single site studies.

In conclusion, in this multi-site study of 330 mechanically ventilated patients with ALI, there was a significant association between the administration of systemic corticosteroids and transition to delirium, even after adjustment for use of sedative medications, relevant patient-specific risk factors, and severity of illness measures. Given the known short- and long-term morbidity and mortality associated with delirium in the ICU, these findings should be considered when weighing potential risk and benefits of using systemic corticosteroids in patients with ALI.

## Acknowledgments

This research was supported by the National Institutes of Health (Acute Lung Injury SCCOR Grant # P050 HL 73994). The funding body had no role in the study design, manuscript writing or decision to submit the manuscript for publication.

Dr. Shanholtz received grant support from NHLBI and support for article research from NIH. His institution received grant support from NHLBI. Dr. Needham received support for article research from NIH. His institution received grant support from NIH.

## References

1. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr. Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA : the journal of the American Medical Association. 2004; 291(14):1753–1762. [PubMed: 15082703]
2. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. Age and ageing. 1999; 28(6):551–556. [PubMed: 10604507]
3. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, Truman B, Bernard GR, Dittus RS, Ely EW. Costs associated with delirium in mechanically ventilated patients. Critical care medicine. 2004; 32(4):955–962. [PubMed: 15071384]
4. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. American journal of respiratory and critical care medicine. 2009; 180(11):1092–1097. [PubMed: 19745202]
5. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Critical care medicine. 2010; 38(7):1513–1520. [PubMed: 20473145]
6. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN. Cognitive trajectories after postoperative delirium. The New England journal of medicine. 2012; 367(1):30–39. [PubMed: 22762316]
7. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009; 373(9678):1874–1882. [PubMed: 19446324]
8. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, Brower RG, Fan E. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality

improvement project. Archives of physical medicine and rehabilitation. 2010; 91(4):536–542. [PubMed: 20382284]

9. Inouye SK, Bogardus ST Jr. Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr. A multicomponent intervention to prevent delirium in hospitalized older patients. The New England journal of medicine. 1999; 340(9):669–676. [PubMed: 10053175]
10. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Risk factors of delirium after cardiac surgery: a systematic review. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2011; 10(4):197–204.
11. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine. 2013; 41(1):263–306. [PubMed: 23269131]
12. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA : the journal of the American Medical Association. 2009; 301(5):489–499. [PubMed: 19188334]
13. Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, Bienvenu OJ, Rowden AM, Touradji P, Brower RG, et al. The Effect of a Quality Improvement Intervention on Perceived Sleep Quality and Cognition in a Medical ICU*. Critical care medicine. 2013; 41(3): 800–809. [PubMed: 23314584]
14. Hager DN, Dinglas VD, Subhas S, Rowden AM, Neufeld KJ, Bienvenu OJ, Touradji P, Colantuoni E, Reddy DR, Brower RG, et al. Reducing Deep Sedation and Delirium in Acute Lung Injury Patients: A Quality Improvement Project. Critical care medicine. 2013
15. Stoudemire A, Anfinson T, Edwards J. Corticosteroid-induced delirium and dependency. General hospital psychiatry. 1996; 18(3):196–202. [PubMed: 8739013]
16. Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry and clinical neurosciences. 2011; 65(6):549–560. [PubMed: 22003987]
17. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics. 2002; 43(3):183–194. [PubMed: 12075033]
18. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. Journal of affective disorders. 1983; 5(4):319–332. [PubMed: 6319464]
19. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, et al. Hydrocortisone therapy for patients with septic shock. The New England journal of medicine. 2008; 358(2):111–124. [PubMed: 18184957]
20. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA : the journal of the American Medical Association. 1998; 280(2):159–165. [PubMed: 9669790]
21. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Critical care medicine. 2009; 37(5):1594–1603. [PubMed: 19325471]
22. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. The New England journal of medicine. 2006; 354(16):1671–1684. [PubMed: 16625008]
23. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ. 2004; 329(7464):480. [PubMed: 15289273]
24. Karir V, Cooke CR, Andersson L, Caldwell E, Rubenfeld GD. Practice variability in the assessment and treatment of critical illness-related corticosteroid insufficiency. Journal of critical care. 2010; 25(2):363, e369–363, e314. [PubMed: 19781894]

25. Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. Clinical therapeutics. 2011; 33(10):1413–1432. [PubMed: 21999885]
26. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Critical care medicine. 2011; 39(2):371–379. [PubMed: 20959786]
27. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosomatic medicine. 2008; 70(4): 512–519. [PubMed: 18434495]
28. Salgado DR, Favory R, Goulart M, Brimioulle S, Vincent JL. Toward less sedation in the intensive care unit: a prospective observational study. Journal of critical care. 2011; 26(2):113–121. [PubMed: 21273035]
29. Needham DM, Wang W, Desai SV, Mendez-Tellez PA, Dennison CR, Sevransky J, Shanholtz C, Ciesla N, Spillman K, Pronovost PJ. Intensive care unit exposures for long-term outcomes research: development and description of exposures for 150 patients with acute lung injury. Journal of critical care. 2007; 22(4):275–284. [PubMed: 18086397]
30. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. American journal of respiratory and critical care medicine. 1994; 149(3 Pt 1):818–824. [PubMed: 7509706]
31. Needham DM, Dennison CR, Dowdy DW, Mendez-Tellez PA, Ciesla N, Desai SV, Sevransky J, Shanholtz C, Scharfstein D, Herridge MS, et al. Study protocol: The Improving Care of Acute Lung Injury Patients (ICAP) study. Crit Care. 2006; 10(1):R9. [PubMed: 16420652]
32. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA : the journal of the American Medical Association. 2001; 286(21):2703–2710. [PubMed: 11730446]
33. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA : the journal of the American Medical Association. 2003; 289(22):2983–2991. [PubMed: 12799407]
34. Brunton, LLLJ.; Parker, KL. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11th edn. McGraw-Hill; New York: 2006.
35. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of clinical epidemiology. 1994; 47(11):1245–1251. [PubMed: 7722560]
36. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006; 104(1):21–26. [PubMed: 16394685]
37. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. Critical care clinics. 2006; 22(2):313–327. [PubMed: 16678002]
38. Greer, N.; Rossom, R.; Anderson, P.; MacDonald, R.; Tacklind, J.; Rutks, I.; Wilt, TJ. Delirium: Screening, Prevention, and Diagnosis - A Systematic Review of the Evidence. Washington (DC): 2011.
39. Noimark D. Predicting the onset of delirium in the post-operative patient. Age and ageing. 2009; 38(4):368–373. [PubMed: 19297372]
40. Aghanwa HS, Ndububa D. Specific psychiatric morbidity in liver cirrhosis in a Nigerian general hospital setting. General hospital psychiatry. 2002; 24(6):436–441. [PubMed: 12490347]
41. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Critical care medicine. 1985; 13(10):818–829. [PubMed: 3928249]
42. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA : the journal of the American Medical Association. 2001; 286(14):1754–1758. [PubMed: 11594901]
43. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Committee ASCC: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of

Chest Physicians/Society of Critical Care Medicine. 1992. Chest. 2009; 136(5 Suppl):e28. [PubMed: 20162763]

44. Wilson WC, Smedira NG, Fink C, McDowell JA, Luce JM. Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. JAMA : the journal of the American Medical Association. 1992; 267(7):949–953. [PubMed: 1370853]
45. Brunton, LBLJ.; Parker, KL. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11 edn. McGraw-Hill; New York: 2005.
46. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Critical care medicine. 2008; 36(2):427–433. [PubMed: 18091554]
47. John, M.; Chambers, WSC.; Paul, A. Tukey, Beat Kleiner: Graphical Methods for Data Analysis. Duxbury Press; 1983.
48. Meyan, S. Markov Chains and Stochastic Stability. 2 edn. Cambridge University Press; 2009.
49. Hosmer, D.; Laemeshow, S. Applied Logistic Regression. Wiley; New York: 2000.
50. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, van der Hoeven JG, Donders R, van Achterberg T, Schoonhoven L. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012; 344:e420. [PubMed: 22323509]
51. Fardet L, Flahault A, Kettaneh A, Tiev KP, Genereau T, Toledano C, Lebbe C, Cabane J. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. The British journal of dermatology. 2007; 157(1):142–148. [PubMed: 17501951]
52. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Am J Psychiatry. 2012; 169(5):491–497. [PubMed: 22764363]
53. Ushida T, Yokoyama T, Kishida Y, Hosokawa M, Taniguchi S, Inoue S, Takemasa R, Suetomi K, Arai YC, McLaughlin M, et al. Incidence and risk factors of postoperative delirium in cervical spine surgery. Spine (Phila Pa 1976). 2009; 34(23):2500–2504. [PubMed: 19927098]
54. Lin SM, Huang CD, Liu CY, Lin HC, Wang CH, Huang PY, Fang YF, Shieh MH, Kuo HP. Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients. Journal of critical care. 2008; 23(3):372–379. [PubMed: 18725043]
55. Micek ST, Anand NJ, Laible BR, Shannon WD, Kollef MH. Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. Critical care medicine. 2005; 33(6):1260–1265. [PubMed: 15942341]
56. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr. Dittus R, Ely EW. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. The Journal of trauma. 2008; 65(1):34–41. [PubMed: 18580517]
57. Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, Ehtisham A, Nold J, Agarwal S, Azocar R, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Critical care medicine. 2009; 37(6):1898–1905. [PubMed: 19384221]
58. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. Critical care medicine. 2009; 37(1):177–183. [PubMed: 19050611]
59. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, Evans DA. Risk factors for delirium in hospitalized elderly. JAMA : the journal of the American Medical Association. 1992; 267(6):827–831. [PubMed: 1732655]
60. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA : the journal of the American Medical Association. 2007; 298(22):2644–2653. [PubMed: 18073360]

61. McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, et al. Delirium in the Cardiovascular ICU: Exploring Modifiable Risk Factors*. Crit Care Med. 2013; 41(2):405–413. [PubMed: 23263581]

62. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. Critical care medicine. 2013; 41(4):999–1008. [PubMed: 23385102]

63. Bienvenu OJ, Gellar J, Althouse BM, Colantuoni E, Sricharoenchai T, Mendez-Tellez PA, Shanholtz C, Dennison CR, Pronovost PJ, Needham DM. Post-traumatic stress disorder symptoms after acute lung injury: a 2-year prospective longitudinal study. Psychological medicine. 2013:1–15.

64. Maldonado J, Wysong A, van der Starre P, Block T, Reitz B. Postoperative sedation can dramatically alter the development of delirium after cardiac surgery. Psychosomatics. 2005; 46(185-6)

65. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, Herr DL, Maze M, Ely EW. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care. 2010; 14(2):R38. [PubMed: 20233428]

## Table 1

Patient Characteristics (n=330)

| Characteristic | Result |
|---|---|
| **Demographics** | |
| Age, median (IQR) years | 51 (41, 63) |
| Male, No. (%) | 183 (55) |
| Caucasian race, No. (%) | 199 (60) |
| Charlson comorbidity index score, median (IQR) | 2 (1, 4) |
| **Comorbidities, No. (%)** | |
| Current or prior illicit drug use | 87 (26) |
| Current or prior excess alcohol use | 79 (24) |
| Prior cerebral vascular accident | 29 (9) |
| **Home Medication Use, No. (%)** | |
| Opioids | 70 (21) |
| Systemic corticosteroids | 45 (14) |
| Benzodiazepines | 29 (9) |
| **Critical Illness** | |
| Medical ICU admission, No. (%) | 231 (70) |
| APACHE II score, median (IQR) | 24 (19, 30) |
| Ever use of continuous hemodialysis, No. (%) | 29 (9) |

Abbreviations: IQR – Inter-quartile Range, ICU – Intensive Care Unit, APACHE II – Acute Physiology and Chronic Health Evaluation II[41] score

**Table 2**

Summary of Daily ICU Variables, by Delirium and Corticosteroid Status[a]

| Variable | "Normal" (Delirium/ Coma-Free), n = 634 | Delirium, n = 99 | No Corticosteroid Administered, n =478 | Corticosteroid Administered , n = 255 |
|---|---|---|---|---|
| Daily SOFA score[b], median (IQR) | 5 (3, 8) | 6 (4, 9) | 5 (2, 7) | 7 (4, 12) |
| Daily Sepsis status, No. (%) | 412 (65) | 62 (63) | 283 (59) | 191 (75) |
| Use of corticosteroids in prior 24 hours, No. (%) | 214 (34) | 41 (41) | - | - |
| Prednisone-equivalent dose (if any use), median (IQR) mg | 23 (13, 50) | 44 (13, 75) | - | - |
| Use of benzodiazepine in prior 24 hours, No. (%) | 183 (29) | 33 (33) | 164 (34) | 52 (20) |
| Midazolam-equivalent dose (if any use), median (IQR) mg | 8 (3, 23) | 10 (5, 28) | 7 (3, 17) | 14 (5, 39) |
| Use of narcotic in prior 24 hours, No. (%) | 372 (57) | 60 (61) | 274 (57) | 158 (62) |
| Morphine-equivalent dose (if any use), median (IQR) mg | 22 (7, 65) | 47 (9, 160) | 27 (8, 84) | 20 (5, 67) |
| Presence of delirium, No. (%) | - | - | 58 (12) | 41 (16) |

Abbreviations: SOFA – Sequential Organ Failure Assessment Score[42] IQR – Inter-quartile Range,

[a]Data are presented for 330 patients with 733 patient days that were included in the analysis of transition to delirium (i.e. "normal" status on previous day). The daily probability of transition to delirium was 14% (99/733). Data for administration of corticosteroids are presented to reflect administration on the 733 days included in this assessment.

[b]SOFA score[42] is modified to exclude the neurologic component to prevent adjusting for a component of the primary outcome within the regression model

## Table 3

Patient and ICU variables associated with transition to delirium

| | Odds Ratio (95% CI) of Transitioning to Delirium[a] | | | |
|---|---|---|---|---|
| **Variable** | **Bivariable Analysis** | **p[b]** | **Multivariable Analysis** | **p[b]** |
| **Patient characteristics** | | | | |
| Age <40 years old | Ref | | Ref | |
| Age 40- 60 years old | 1.65 (1.17, 2.32) | < 0.01 | 1.81 (1.26, 2.62) | 0.002 |
| Age >60 years old | 2.18 (1.37, 3.47) | < 0.001 | 2.52 (1.65, 3.87) | < 0.001 |
| Male | 1.31 (0.94, 1.82) | 0.11 | 1.34 (0.96, 1.86) | 0.08 |
| Caucasian race | 0.79 (0.57, 1.10) | 0.17 | 0.74 (0.53, 1.02) | 0.06 |
| Charlson comorbidity index score | 1.04 (0.97, 1.11) | 0.25 | | |
| Current or prior illicit drug abuse | 1.16 (0.64, 2.10) | 0.62 | | |
| Current or prior excess alcohol use | 1.16 (0.81, 1.67) | 0.42 | | |
| Prior cerebral vascular accident | 1.29 (0.71, 2.37) | 0.41 | | |
| Home use of Opioids | 1.15 (1.01, 1.31) | 0.04 | 1.11 (0.97, 1.27) | 0.12 |
| Home use of systemic corticosteroids | 0.89 (0.72, 1.12) | 0.32 | | |
| Home use of benzodiazepines | 1.04 (0.84, 1.28) | 0.74 | | |
| **ICU-related characteristics** | | | | |
| Medical ICU admission | 0.87 (0.57, 1.31) | 0.49 | | |
| APACHE II score at ICU admission | 1.01 (1.00, 1.03) | 0.10 | 1.01 (1.00, 1.03) | 0.31 |
| Use of continuous hemodialysis, ever | 1.08 (0.69, 1.71) | 0.73 | | |
| Daily SOFA score[c] | 1.05 (1.01, 1.09) | 0.02 | 1.03 (0.99, 1.07) | 0.11 |
| Daily sepsis status | 1.25 (0.93, 1.67) | 0.14 | 1.06 (0.79, 1.41) | 0.71 |
| Corticosteroid Administration | 1.48 (1.05, 2.08) | 0.03 | 1.52 (1.05, 2.21) | 0.03 |
| Higher Corticosteroid dose (per 40mg prednisone equivalent in 24h) | 1.03 (0.94, 1.13) | 0.56 | 0.97 (0.89, 1.07) | 0.57 |
| Benzodiazepine Administration | 1.33 (1.01, 1.75) | 0.05 | 1.32 (0.93, 1.89) | 0.12 |
| Higher Benzodiazepine dose (per 5mg midazolam equivalent in 24h) | 1.02 (0.99, 1.04) | 0.13 | 1.02 (0.99, 1.04) | 0.18 |
| Opioid Administration | 1.16 (0.88, 1.52) | 0.29 | | |

Abbreviations: CI, confidence interval, ICU – Intensive Care Unit, APACHE II – Acute Physiology and Chronic Health Evaluation II[41] score, SOFA, Sequential Organ Failure Assessment score[42]

[a] Odds Ratios are interpreted as the odds of a transition to a delirious state from a normal state given the characteristic (for binary exposures) or given a one unit increase (for continuous exposures)

[b] p values calculated using multivariate logistic regression adjusted for delirium status on the previous day, with robust variance estimates for repeated measures on the same subject.

[c] SOFA score[42] is modified to exclude the neurologic component to prevent adjusting for a component of the primary outcome within the regression model