Published in final edited form as:

Crit Care Med. 2008 October ; 36(10): 2726–2733. doi:10.1097/CCM.0b013e31818781f5.

Intensive Care Unit Hypoglycemia Predicts Depression during Early Recovery from Acute Lung Injury

David W. Dowdy, ScM^{1,2}, Victoriano Dinglas, BS³, Pedro A. Mendez-Tellez, MD⁴, O. Joseph Bienvenu, MD, PhD⁵, Jonathan Sevransky, MD³, Cheryl R. Dennison, PhD⁶, Carl Shanholtz, MD⁷, and Dale M. Needham, MD, PhD^{3,*}

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

²School of Medicine, Johns Hopkins University, Baltimore, MD, USA

³Division of Pulmonary/Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA

⁴Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA

⁵Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

⁶Johns Hopkins School of Nursing, Baltimore, MD, USA

⁷Division of Pulmonary/Critical Care Medicine, University of Maryland, Baltimore, MD, USA

Abstract

Objective—To evaluate the association between intensive care unit (ICU) blood glucose levels and depression following acute lung injury (ALI)

Design—Prospective cohort study

Setting—Twelve ICUs in 4 hospitals in Baltimore, MD

Patients—Consecutive ALI survivors (n = 104) monitored during 1,717 ICU patient-days and screened for depression at three months after ALI

Interventions—None

Measurements and Main Results—The prevalence of a positive screening test for depression (Hospital Anxiety and Depression [HAD] depression sub-scale score ≥ 8) at follow-up was 28%. After adjustment for confounders, patients with a mean daily minimum ICU glucose <100 mg/dL had significant increases in mean depression score [2.1 points, 95% confidence interval (CI) 0.6 – 3.7] and in the likelihood of a positive depression screening test [relative risk (RR) 2.6, 95% CI 1.2 – 4.2]. Patients with documented hypoglycemia <60 mg/dL during their ICU stay also had greater symptoms of depression (2.0 points, 95% CI 0.5 – 3.5; RR 3.6, 95% CI 1.8 – 5.1). Other factors independently associated with a positive depression screening test included body mass index >40 kg/m² (RR 3.3, 95% CI 1.2 – 4.2), baseline depression/anxiety (RR 3.9, 95% CI 1.5 – 6.5), and mean daily ICU benzodiazepine dose >100 mg of midazolam-equivalent (RR 2.4, 95% CI 1.1 – 3.8).

Conclusions—Hypoglycemia in the ICU is associated with an increased risk of positive screening for depression during early recovery from ALI. Baseline depressive symptoms, morbid obesity, and ICU benzodiazepine dose were also associated with post-ALI depressive symptoms. These findings

*Address for Correspondence (Reprints will not be ordered): Dale M. Needham, MD, PhD, Pulmonary & Critical Care Medicine, Johns Hopkins University, Baltimore, MD 21205, dale.needham@jhmi.edu, Ph: 410-955-3467, Fax: 410-955-0036.

The authors have not disclosed any potential conflicts of interest.

warrant increased glucose monitoring for ICU patients at risk for hypoglycemia and further research on how patient and ICU management factors may contribute to post-ICU depression.

Keywords

hypoglycemia; depression; intensive care units; respiratory distress syndrome; adult; critical care; blood glucose

Introduction

Dysregulation of blood glucose during critical illness has a negative impact on patient outcomes. Patients randomized to tight glycemic control, versus permissive hyperglycemia, have improved intensive care unit (ICU) survival (1,2) and long-term morbidity (3-5). Similarly, intensive care unit (ICU) hypoglycemia is an independent risk factor for mortality in some studies (6,7), although its full consequences remain less clear (8). In the ICU, it is difficult to avoid hyperglycemia without increasing the risk of hypoglycemia (9). In striking a balance between hyper- and hypoglycemia, it is important to understand the associated morbidities, particularly the neuro-psychiatric effects of glucose levels during critical illness.

The brain is sensitive to both the metabolic restrictions of hypoglycemia (10,11) and the detrimental effects of hyperglycemia (12-14). In patients with diabetes mellitus, both hyperglycemia (15) and hypoglycemia (16,17) are associated with a higher prevalence of depression. It is unclear whether similar associations hold for critically ill patients who experience wide variations in blood glucose during their ICU stay (18) and also have a high prevalence of depressive symptoms during their subsequent recovery (19-21). Among critically ill patients, those with acute lung injury (ALI) may be especially sensitive to the effects of blood glucose, given their high severity of illness, long ICU stay, and frequent long-term morbidity (12,22,23). We hypothesized that such effects would be most pronounced during early recovery, when patients are no longer critically ill, but have not yet experienced many post-ICU events that could influence their psychiatric condition. Thus, we investigated the association of ICU blood glucose levels with symptoms of depression at three months after the diagnosis of ALI.

Materials and Methods

Study Population

The study population is drawn from the Improving Care of Acute Lung Injury Patients (ICAP) study, an ongoing prospective cohort study of the long-term physical and mental health outcomes of ALI survivors. Details of the study protocol have been published elsewhere (24). In brief, the ICAP study prospectively collects clinical data for consecutive, mechanically ventilated patients with ALI, as defined by the American-European consensus conference (25), at 12 ICUs in 4 hospitals in Baltimore, MD. To avoid inclusion of ALI patients with primary neurological illness or trauma, patients in neurological ICUs at the participating study site hospitals were not enrolled. The present analysis includes all participants who were diagnosed with ALI before January 7, 2007. Key exclusion criteria include: (1) pre-existing illness with a life expectancy of <6 months; (2) known cognitive impairment; (3) communication or language barrier; (4) transfer into study site ICU with pre-existing ALI of >24 hours duration; (5) >5 days of mechanical ventilation before ALI; (6) no fixed address; and (7) limitations in ICU care (e.g., no use of vasopressors). Patient demographics (age, gender, race), height, weight, and Acute Physiology and Chronic Health Evaluation (APACHE) II severity of illness score (26) are obtained upon admission to the study site ICU. Sequential Organ Failure Assessment (SOFA) score (27), plus the dose, route and frequency of administration of selected medications (including insulin, corticosteroids, narcotics, and

benzodiazepines) are collected daily after ALI diagnosis while patients were in the ICU. Antidepressant use was not measured. Co-morbid conditions (e.g., diabetes mellitus) are abstracted from the medical record. Patients' functional status (independence in activities of daily living [ADLs]) (28), years of formal education, and employment status prior to hospitalization (including health-related employment restrictions) are collected by interview with the patient (or proxy, when unable to obtain patient response). Patients' mood symptoms prior to hospital admission are assessed retrospectively using the depression/anxiety dimension of the EQ-5D quality of life instrument (29), modified to elicit patients' self-reported depression or anxiety immediately before the onset of the illness that caused hospital admission. In the present analysis, a response of "moderate" or "extreme" depression/anxiety (versus "none") was considered a positive response for abnormal baseline mood symptoms. Age, ICU length of stay, and APACHE II and SOFA scores were modeled as continuous variables while all other continuous exposures were modeled as tertiles using clinically relevant thresholds closest to the 33rd and 67th percentile in order to characterize nonlinear associations and prevent undue influence from outlying observations.

Measurement of Blood Glucose in the ICU

To evaluate hypoglycemia and hyperglycemia, we prospectively collected three distinct measures of blood glucose on a daily basis during eligible patients' ICU stay: 24-hour minimum, 24-hour maximum, and the average of values taken at 6AM and 6PM (± 2 hours). For each measure of blood glucose, we calculated patients' mean value over their entire ICU stay and stratified patients into tertiles (with thresholds rounded to the nearest multiple of 5 mg/dL). We also conducted an *a priori* secondary analysis of hypoglycemia, defined as any glucose value < 60 mg/dL during patients' ICU stay (30). Multiple episodes of hypoglycemia occurring on a single day were not separately recorded.

Measurement of Depression after Discharge

The primary outcome of this analysis was depression, measured at three months after ALI, as a continuous variable using the depression sub-scale of the Hospital Anxiety and Depression (HAD) instrument (31). This sub-scale includes seven items with a total score ranging from 0 to 21. Higher scores indicate greater symptoms of depression. In a secondary analysis, we used a binary measure of depression as the outcome, defined *a priori* using a standard cut-off threshold for the HAD depression sub-scale of ≥ 8 , with sensitivity analyses performed using the alternative higher threshold of ≥ 11 (31). Although the HAD is a validated instrument, it does not permit a clinical diagnosis of depression, which would require clinical psychiatric interviews.

Statistical Analysis

We compared the distribution of all exposure variables across tertiles of mean ICU glucose using Fisher's exact test (categorical variables) and the global F-test from analysis of variance (ANOVA) (continuous variables). For each exposure variable, we calculated univariable p-values for the association with mean depression score using linear least-squares regression, and for the association with a positive depression screening test (HAD depression sub-scale score ≥ 8) using Fisher's exact test (categorical exposures) or logistic regression (continuous exposures). All exposure variables (Table 1) having a crude association with depression at $p \leq 0.15$ were analyzed in multivariable linear and logistic regression models. Missing data (which occurred only for education and baseline mood symptoms) were imputed using best-subset regression (32). To avoid overestimating the magnitude of the association between exposure variables and depression (which had a high prevalence in our patient sample), we converted odds ratios from logistic regression into relative risks using the Zhang and Yu method (33). Sequential removal of variables other than the primary exposure (to evaluate for

model over-fitting) and removal of patients with missing data (to evaluate the impact of imputation) did not materially change the association between the primary exposure and depression.

Potentially important statistical interactions of blood glucose with selected exposure variables were decided on an *a priori* basis and evaluated by including multiplicative terms in unadjusted linear regression models of mean depression score. Influence was evaluated using added-variable plots; the effect of outlier data values on regression coefficients was estimated using Dfbeta statistics; and collinearity was assessed using variance inflation factors (32,34). Goodness-of-fit was evaluated using the Hosmer-Lemeshow statistic for logistic models. All p-values were two-sided, with statistical significance defined as $p < 0.05$. Analyses were performed using STATA version 9.2 (Stata Corp., College Station, TX, USA).

The ICAP study was approved by the Institutional Review Boards of all participating institutions.

Results

Of 366 eligible patients, 191 (52%) survived hospitalization, of whom 135 were still alive and consented for follow-up at three months after ALI diagnosis (Figure 1). At follow-up, 15 patients (11%) were incapable of completing the depression questionnaire due to severe cognitive, physical or other impairments, and 16 (12%) missed their appointment, resulting in complete depression surveys on 104 patients. Compared to the 104 included patients, these 31 three-month survivors not completing follow-up had a higher mean daily ICU maximum glucose (172 vs. 152 mg/dL, $p = 0.01$) and a higher proportion experiencing hyperglycemia (71% vs. 50% with ≥ 1 measurement > 210 mg/dL), but did not significantly differ with respect to mean daily ICU minimum glucose (108 vs. 104 mg/dL, $p = 0.26$) or proportion experiencing hypoglycemia (48% vs. 32% with ≥ 1 measurement < 60 mg/dL, $p = 0.13$). None of the included patients' medical records reported a history of "stroke," cerebrovascular accident (CVA), or transient ischemic attack (TIA).

Patient exposures, including baseline characteristics, ICU course, and glucose measures, were collected during 1,717 ICU patient-days (Table 1). When evaluating these exposures across tertiles of mean daily glucose, patients with higher glucose had significantly greater body mass index (BMI), higher prevalence of diabetes, and lower prevalence of mood symptoms at baseline; in the ICU, these patients received higher doses of insulin and steroids (Table 1). Patients with lower mean glucose had a significantly lower mean daily minimum glucose, but did not have a significantly increased likelihood of experiencing at least one episode of hypoglycemia (< 60 mg/dL). Hypoglycemia < 60 mg/dL occurred in 33 (32%) patients, 12 (36%) of whom experienced hypoglycemia on > 1 ICU day.

At follow-up, the mean HAD depression score was 5.5 (95% confidence interval [CI] 4.8 – 6.3), and the prevalence of a positive screening test for depression was 28% (95% CI 19 – 37%) using a HAD threshold of ≥ 8 points, or 11% (4 – 17%) using ≥ 11 points. The lowest tertile of mean daily minimum blood glucose (< 100 mg/dL) was associated with worse depression outcomes ($p < 0.01$), while there was no association of depression screening results with mean or maximum blood glucose measures (Figure 2). Accordingly, all subsequent analyses of glucose and depression were restricted to measures of low blood glucose, with the primary exposure being mean daily minimum glucose < 100 mg/dL (vs. ≥ 100 mg/dL). Sensitivity analyses conducted by varying the threshold for minimum glucose (in increments of 5 mg/dL) revealed that its association with a positive depression screening test was significant ($p < 0.01$) and similar in magnitude at all threshold values between 80 mg/dL and 100 mg/dL.

In multivariable regression models, mean daily minimum glucose <100 mg/dL was associated with both HAD depression score (mean increase: 2.1, 95% CI 0.6 – 3.7) (Table 2) and prevalence of a positive depression screening test (relative risk [RR] for HAD $\geq$ 8: 2.6; 95% CI 1.2 – 4.2) (Table 3). The occurrence of hypoglycemia (<60 mg/dL) had a similar association with depression score (mean increase: 2.0, 95% CI 0.5 – 3.5, $p = 0.007$) and a positive depression screening test (RR for HAD $\geq$ 8: 3.6; 95% CI 1.8 – 5.1, $p = 0.001$). Other factors associated with both depression score (Table 2) and a positive depression screen (Table 3) included morbid obesity (BMI >40 kg/m²) (RR 3.3, 95% CI 1.2 – 4.2) and symptoms of depression/anxiety prior to ICU admission (RR 3.9, 95% CI 1.5 – 6.5). Mean daily benzodiazepine dose >100 mg/day of midazolam-equivalent was associated with a positive depression screening test (RR 2.4, 95% CI 1.1 – 3.8; Table 3), but not with the mean HAD depression score.

The associations of minimum glucose and hypoglycemia with the HAD depression score demonstrated a significant ($p=0.01$) interaction (Figure 3). Patients with both low minimum glucose and hypoglycemia had significantly elevated depression scores (mean increase 4.0, 95% CI 2.4 – 5.7) and prevalence (RR 3.9, 95% CI 1.9 – 7.7). Diabetes status, baseline symptoms of anxiety/depression, ICU length of stay, and benzodiazepine dose did not demonstrate a significant interaction with minimum glucose on depression score ($p \geq 0.3$ for each comparison).

Discussion

In this prospective observational study, measures of low blood glucose in the ICU were significantly associated with depressive symptoms at 3 months after acute lung injury. Mean daily minimum glucose <100 mg/dL was independently associated with a 2.6-fold increased risk of depression (HAD depression score $\geq$ 8), and documented hypoglycemia (<60 mg/dL) was associated with a 3.6-fold increased risk. Patients with both low minimum glucose and hypoglycemia experienced the greatest risk for depressive symptoms. These findings suggest that hypoglycemia during critical illness is associated with depression during ALI survivors' early recovery.

The 28% prevalence of a positive depression screening test at 3 months after ALI in this study is similar to prevalence rates of 25% – 32% reported in other populations of mechanically ventilated patients (35-37), and substantially higher than the 8% prevalence of depression (using HAD depression score $\geq$ 8) in a general adult population (38). Similarly, when defining hypoglycemia as <40 mg/dL, as done in a large randomized trial of tight glycemic control in a medical ICU (6), our rates (6% in patients not on insulin infusion protocol, 24% on protocol) were very similar to that trial (4%, 25%). Because of our limited number of patients with hypoglycemia <40 mg/dL ($n = 9$), we did not analyze these patients separately. However, these patients had similar levels of depressive symptoms, whether measured by mean HAD score or prevalence of scores $\geq$ 8, to the 24 hypoglycemic patients with glucose values between 41 and 59 mg/dL ($p > 0.7$ for comparison of each outcome).

Our findings suggest that depressive symptoms are more strongly associated with a combination of documented hypoglycemia and low daily minimum glucose than with either factor alone. Specifically, documented hypoglycemia may be most strongly associated with depressive symptoms in patients whose daily minimum values have also been low during their ICU stay. Low minimum glucose may reflect additional episodes of undetected hypoglycemia, especially since commonly used capillary blood glucose measurements may overestimate serum values in ICU patients (39,40). Thus, intensified glucose monitoring may be justified for patients at risk for hypoglycemia, such as those with diabetes mellitus, changing nutritional

intake, continuous renal replacement therapy, sepsis, and insulin infusion protocols for tight glycemic control (7,11,30,41,42).

To our knowledge, this is the first study to investigate the association of ICU blood glucose with depression after critical illness. Follow-up from van den Berghe and colleagues' trial (4) suggested that ICU hypoglycemia (<40 mg/dL) was not associated with persistently altered neurological status, epilepsy, and coma at hospital discharge, or with diminished performance status at 4 years (2). However, an association with psychiatric symptoms was not reported.

Our results add to the growing body of evidence that patients' condition and management while in the ICU may have an important impact on their outcomes after hospital discharge. Prior studies have found associations of ICU hypoxia with neurocognitive impairments at hospital discharge (12) and duration of sedative administration with post-discharge depression (43). This latter finding is corroborated by our observation that mean daily ICU benzodiazepine dose was significantly associated with a positive depression screening test, independent of patients' baseline depression/anxiety status. Future studies of critically ill patients should consider measuring post-discharge neuropsychiatric outcomes in survivors to further explore these relationships.

This research has a number of potential limitations. First, as an observational study, we cannot infer a cause-effect relationship between ICU glucose and depression. Glucose may be a physiological marker of other processes contributing to post-discharge depression, rather than a causal factor itself. Further research is required to elucidate a causal mechanism. However, we did measure and adjust for relevant potential confounders, including other risk factors for depression (e.g., baseline mood symptoms, baseline functional status (44), benzodiazepine use (43)). Second, our hospital mortality rate was high (48%), but comparable to other observational studies of ALI patients (45-47) and lower than the mean predicted mortality rate (55%, 95% confidence interval 52 – 59%) based on our patients' high APACHE II severity of illness scores (26). Third, we measured mood symptoms at baseline using the single-item EQ-5D depression/anxiety dimension, and at follow-up with the seven-item HAD depression sub-scale. While both instruments have been independently validated, they do not constitute a clinical diagnosis of depression, suggesting a need for further studies employing clinical assessments of depression in ICU survivors. Fourth, we limited our study to depressive symptoms and cannot comment on the association of ICU glucose levels with other potentially important outcomes, including neuromuscular dysfunction (48) and post-traumatic stress (19,21). Fifth, although patients with known cognitive impairment prior to hospitalization were excluded from the study, we did not collect detailed data on cognitive impairment or antidepressant use at follow-up; this may have affected our 3-month assessments of patients' depression symptoms. Although patients with lower post-ICU cognitive function might be expected to have worse depression scale scores, one prior study (12) found no association between cognitive impairment and symptoms of depression in ALI survivors. Finally, we measured only daily minimum, maximum, and 6AM/6PM glucose values between ALI diagnosis and ICU discharge. Thus, we could not fully capture all relevant hypoglycemic events (e.g., repeat events in one day, prolonged events, or those occurring either before ALI diagnosis or after ICU discharge) that may have contributed to post-discharge depressive symptoms. However, our primary exposure (mean minimum daily glucose) was prospectively collected and available for 1,712 (99.7%) of 1,717 eligible patient-days, and any under-recognition of low blood glucose would likely bias our results toward the null hypothesis of no association.

Conclusions

This observational study of 104 ALI survivors over 1,717 days of ICU care suggests that ICU hypoglycemia is strongly associated with symptoms of depression during patients' early

recovery from critical illness. Other factors associated with post-ALI depressive symptoms include baseline mood, morbid obesity, and ICU benzodiazepine dose. These findings warrant increased glucose monitoring for ICU patients at risk for hypoglycemia, and further research on how patient and ICU management factors contribute to post-ICU depression.

Acknowledgements

We thank all patients who participated in the study and the dedicated research staff who assisted with the study: Ms. Rachel Bell, Ms. Kim Boucher, Dr. Sanjay Desai, Ms. Carinda Feild, Ms. Thelma Harrington, Dr. Praveen Kondreddi, Ms. Frances Magliacane, Ms. Elizabeth Miller, Ms. Stacey Murray, Dr. Kim Nguyen, Dr. Susanne Prassl, Dr. Al Salem, Ms. Arabella Sampaio, Ms. Kristin Sepulveda, Dr. Shabana Shahid, and Ms. Michelle Silas.

This research is supported by the National Institutes of Health (Acute Lung Injury SCCOR Grant # P050 HL 73994). Mr. Dowdy is supported by the National Institutes of Health, Medical Scientist Training Program Award (T32 GM07309). Drs. Dennison, Bienvenu, and Sevransky are supported by Mentored Patient-Oriented Research Career Development Awards from the National Institutes of Health (K23 NR009193, K23 MH64543, and K23 GM071399, respectively). Dr. Needham is supported by a Clinician-Scientist Award from the Canadian Institutes of Health Research. The funding bodies had no role in the study design, manuscript writing or decision to submit the manuscript for publication.

References

1. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359–1367. [PubMed: 11794168]
2. Ingels C, Debaveye Y, Milants I, et al. Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. *Eur Heart J* 2006;27:2716–2724. [PubMed: 16608860]
3. van den Berghe G, Schoonheydt K, Becx P, et al. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 2005;64:1348–1353. [PubMed: 15851721]
4. van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006;55:3151–3159. [PubMed: 17065355]
5. Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med* 2007;175:480–489. [PubMed: 17138955]
6. van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449–461. [PubMed: 16452557]
7. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007;35:2262–2267. [PubMed: 17717490]
8. Mechanick JI, Handelsman Y, Bloomgarden ZT. Hypoglycemia in the intensive care unit. *Curr Opin Clin Nutr Metab Care* 2007;10:193–196. [PubMed: 17285009]
9. Krinsley JS. Glycemic control in critically ill patients: Leuven and beyond. *Chest* 2007;132:1–2. [PubMed: 17625075]
10. Jones TW, McCarthy G, Tamborlane WV, et al. Mild hypoglycemia and impairment of brain stem and cortical evoked potentials in healthy subjects. *Diabetes* 1990;39:1550–1555. [PubMed: 2245879]
11. Nasraway SA Jr. Sitting on the horns of a dilemma: avoiding severe hypoglycemia while practicing tight glycemic control. *Crit Care Med* 2007;35:2435–2437. [PubMed: 17885378]
12. Hopkins RO, Weaver LK, Collingridge D, et al. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005;171:340–347. [PubMed: 15542793]
13. Bruno A, Biller J, Adams HP Jr, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurology* 1999;52:280–284. [PubMed: 9932944]
14. Yip PK, He YY, Hsu CY, et al. Effect of plasma glucose on infarct size in focal cerebral ischemia-reperfusion. *Neurology* 1991;41:899–905. [PubMed: 2046937]
15. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000;23:934–942. [PubMed: 10895843]

16. Strachan MW, Deary IJ, Ewing FM, et al. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. *Diabetes Care* 2000;23:305–312. [PubMed: 10868856]
17. Wredling RA, Theorell PG, Roll HM, et al. Psychosocial state of patients with IDDM prone to recurrent episodes of severe hypoglycemia. *Diabetes Care* 1992;15:518–521. [PubMed: 1499468]
18. Shulman R, Finney SJ, O'sullivan C, et al. Tight glycaemic control: a prospective observational study of a computerised decision-supported intensive insulin therapy protocol. *Crit Care* 2007;11:R75. [PubMed: 17623086]
19. Scragg P, Jones A, Fauvel N. Psychological problems following ICU treatment. *Anaesthesia* 2001;56:9–14. [PubMed: 11167429]
20. Sukantarat KT, Williamson RC, Brett SJ. Psychological assessment of ICU survivors: a comparison between the Hospital Anxiety and Depression scale and the Depression, Anxiety and Stress scale. *Anaesthesia* 2007;62:239–243. [PubMed: 17300300]
21. Weinert C. Epidemiology and treatment of psychiatric conditions that develop after critical illness. *Curr Opin Crit Care* 2005;11:376–380. [PubMed: 16015119]
22. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–693. [PubMed: 12594312]
23. Dowdy DW, Eid MP, Dennison CR, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med* 2006;32:1115–1124. [PubMed: 16783553]
24. Needham DM, Dennison CR, Dowdy DW, et al. Study protocol: The Improving Care of Acute Lung Injury Patients (ICAP) study. *Crit Care* 2006;10:R9. [PubMed: 16420652]
25. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824. [PubMed: 7509706]
26. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–829. [PubMed: 3928249]
27. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–710. [PubMed: 8844239]
28. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA* 1963;185:914–919. [PubMed: 14044222]
29. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990;16:199–208. [PubMed: 10109801]
30. Oeyen SG, Hoste EA, Roosens CD, et al. Adherence to and Efficacy and Safety of an Insulin Protocol in the Critically Ill: A Prospective Observational Study. *Am J Crit Care* 2007;16:599–608. [PubMed: 17962504]
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–370. [PubMed: 6880820]
32. STATA Corp. STATA reference manual: release 8. College Station, TX: STATA Corp.,; 2003.
33. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690–1691. [PubMed: 9832001]
34. Belsley, D.; Kuh, E.; Welsch, R. *Regression Diagnostics*. New York: John Wiley & Sons; 1980.
35. Hopkins RO, Weaver LK, Chan KJ, et al. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc* 2004;10:1005–1017. [PubMed: 15803563]
36. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med* 2004;32:61–69. [PubMed: 14707560]
37. 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. [PubMed: 12682497]
38. Crawford JR, Henry JD, Crombie C, et al. Normative data for the HADS from a large non-clinical sample. *Br J Clin Psychol* 2001;40:429–434. [PubMed: 11760618]

39. Kanji S, Buffie J, Hutton B, et al. Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005;33:2778–2785. [PubMed: 16352960]
40. Mann EA, Pidcoke HF, Salinas J, et al. Accuracy of glucometers should not be assumed. *Am J Crit Care* 2007;16:531–532. [PubMed: 17962493]
41. Vriesendorp TM, van Santen S, DeVries JH, et al. Predisposing factors for hypoglycemia in the intensive care unit. *Crit Care Med* 2006;34:96–101. [PubMed: 16374162]
42. Vanhorebeek I, Langouche L, van den Berghe G. Tight glucose control: what is the evidence? *Crit Care Med* 2007;35(Suppl):S496–S502. [PubMed: 17713399]
43. Nelson BJ, Weinert CR, Bury CL, et al. Intensive care unit drug use and subsequent quality of life in acute lung injury patients. *Crit Care Med* 2000;28:3626–3630. [PubMed: 11098964]
44. Weinert C, Meller W. Epidemiology of depression and antidepressant therapy after acute respiratory failure. *Psychosomatics* 2006;47:399–407. [PubMed: 16959928]
45. Vincent JL, Zambon M. Why do patients who have acute lung injury/acute respiratory distress syndrome die from multiple organ dysfunction syndrome? Implications for management. *Clin Chest Med* 2006;27:725–731. [PubMed: 17085258]
46. Sakr Y, Vincent JL, Reinhart K, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005;128:3098–3108. [PubMed: 16304249]
47. Luecke T, Muench E, Roth H, et al. Predictors of mortality in ARDS patients referred to a tertiary care centre: a pilot study. *Eur J Anaesthesiol* 2006;23:403–410. [PubMed: 16469204]
48. Stevens RD, Dowdy DW, Michaels RK, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med* 2007;33:1876–1891. [PubMed: 17639340]

Figure 1. Study Flow Diagram

ALI, acute lung injury; ICU, intensive care unit

Figure 2. Depression during Early Recovery from Acute Lung Injury, by ICU Blood Glucose Levels
Bars show the proportion of patients with depressive symptoms by severity (gray, depression score ≥ 8 ; black, depression score ≥ 11). Lines show mean depression scores with 95% confidence intervals. Blood glucose (mg/dL) is depicted in tertiles according to mean ICU value (Figure 2A), mean daily minimum value (Figure 2B), and mean daily maximum value (Figure 2C) in the ICU. *, $p < 0.05$ for comparison with the highest tertile of mean ICU blood glucose; **, $p < 0.01$ for all pairwise comparisons with other tertiles. HAD, Hospital Anxiety and Depression scale.

Figure 3. Effect of Documented Hypoglycemia and Mean Daily Minimum ICU Blood Glucose on Depression during Early Recovery from Acute Lung Injury

Bars show the proportion of patients with depressive symptoms, according to severity (gray, depression score ≥ 8 ; black, depression score ≥ 11). Lines show mean depression scores with 95% confidence intervals. Hypoglycemia is defined as a documented blood glucose < 60 mg/dL during ICU stay. Relative risks were calculated for a depression score ≥ 8 . *, $p < 0.01$ for all pairwise comparisons with other groups; **, $p \leq 0.001$ for all pairwise comparisons with other groups. HAD, Hospital Anxiety and Depression; ICU, intensive care unit.

Table 1
Patient Characteristics, by Tertile of Mean ICU Daily Glucose^a

Variable	Mean ICU Daily Glucose (mg/dL) ^b			Total (n = 104)	P value ^c
	<115 (n = 31)	115-130 (n = 39)	>130 (n = 34)		
Characteristics Prior to ICU Admission					
Age, years	45 (14)	52 (11)	47 (15)	48 (14)	0.14
Male	21 (68%)	16 (41%)	19 (56%)	56 (54%)	0.09
Race					
Caucasian	16 (52%)	26 (67%)	19 (56%)	61 (59%)	0.29
African-American	15 (48%)	13 (33%)	13 (38%)	41 (39%)	
Other	0 (0%)	0 (0%)	2 (6%)	2 (2%)	
Education, years (n=97)					
<12	12 (40%)	10 (27%)	7 (23%)	29 (30%)	0.43
12	8 (27%)	13 (35%)	7 (23%)	28 (29%)	
>12	10 (33%)	14 (38%)	16 (53%)	40 (41%)	
Employment (n = 102) ^d					
Employed	12 (39%)	13 (34%)	16 (48%)	41 (40%)	0.44
Disabled	12 (39%)	10 (26%)	9 (27%)	31 (30%)	
Other	7 (23%)	15 (39%)	8 (24%)	30 (29%)	
BMI (kg/m ²)					
<25	15 (48%)	9 (23%)	8 (24%)	32 (31%)	0.002
25-30	13 (42%)	12 (31%)	9 (26%)	34 (33%)	
30-40	1 (3%)	16 (41%)	12 (35%)	29 (28%)	
>40	2 (6%)	2 (5%)	5 (15%)	9 (9%)	
Diabetes mellitus	1 (3%)	4 (10%)	12 (35%)	17 (16%)	0.001
Dependent in ≥1 activity of daily living (n = 97) ^e	3 (10%)	8 (21%)	6 (20%)	17 (18%)	0.50
Depression/anxiety ^f (n = 87)					
None	10 (40%)	15 (43%)	19 (70%)	44 (51%)	0.04
Moderate	11 (44%)	16 (46%)	7 (26%)	34 (39%)	
Extreme	4 (16%)	4 (11%)	1 (4%)	9 (10%)	
Characteristics of ICU Course					
Type of ICU					
Medical	23 (74%)	29 (74%)	27 (79%)	79 (76%)	0.72
Surgical	6 (19%)	7 (18%)	3 (9%)	16 (15%)	
Trauma	2 (6%)	3 (8%)	4 (12%)	9 (9%)	
ICU length of stay, days	19 (13)	19 (13)	15 (9)	18 (12)	0.31
APACHE II score ^g	23 (6)	23 (6)	25 (7)	24 (6)	0.17
Worst SOFA score ^h	8.5 (3.6)	9.1 (2.6)	8.9 (3.4)	8.8 (3.1)	0.76
ICU Medications (mean daily dose)					
Insulin					
None	13 (42%)	6 (15%)	2 (6%)	21 (20%)	<0.001
≤10 units/day	14 (45%)	19 (49%)	9 (26%)	42 (40%)	
>10 units/day	4 (13%)	14 (36%)	23 (68%)	41 (39%)	
On infusion protocol	2 (6%)	6 (15%)	9 (26%)	17 (16%)	0.09
Steroids (prednisone equivalent)					
None	18 (58%)	17 (44%)	9 (26%)	44 (42%)	0.15
≤50 mg/day	11 (35%)	15 (38%)	16 (47%)	42 (40%)	
>50 mg/day	2 (6%)	7 (18%)	9 (26%)	18 (17%)	
Narcotics (morphine equivalent)					
<50 mg/day	4 (13%)	11 (28%)	13 (38%)	28 (27%)	0.36
50-150 mg/day	16 (52%)	15 (38%)	9 (26%)	40 (38%)	
>150 mg/day	11 (35%)	13 (33%)	12 (35%)	36 (35%)	
Benzodiazepines (midazolam equivalent)					
<25 mg/day	7 (23%)	16 (41%)	9 (26%)	32 (31%)	

Variable	Mean ICU Daily Glucose (mg/dL) ^b		Total (n = 104)	P value ^c
	<115 (n = 31)	>130 (n = 34)		
25-100 mg/day	14 (45%)	17 (50%)	43 (41%)	
>100 mg/day	10 (32%)	8 (24%)	29 (28%)	
<i>Measures of Low Glucose in the ICU</i>				
Any hypoglycemia (<60 mg/dL)	13 (42%)	9 (26%)	33 (32%)	0.36
Mean daily minimum glucose (mg/dL)				
<100	19 (61%)	6 (18%)	38 (37%)	<0.001
100-110	11 (35%)	9 (26%)	35 (34%)	
>110	1 (3%)	19 (56%)	31 (30%)	

ICU, intensive care unit; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

^aValues reported as mean (standard deviation) or n (%). Unless otherwise specified, sample size for all comparisons is 104 patients.

^bPercentages in cells may not add to 100% due to rounding.

^cFisher's exact test or F-test using analysis of variance (ANOVA), across all tertiles.

^d"Disabled" refers to patients who were unemployed due to health problems. "Other" includes students, homemakers, retired persons, and patients who were unemployed for non-health-related reasons.

^eSix items describing pre-ICU functional status: bathing, dressing, toileting, transferring, continence, and feeding (28). Proxies were asked when patients could not respond.

^fPer EQ-5D quality of life survey (29) administered retrospectively to patients before hospital discharge.

^gThis severity of illness score ranges from 0 (best) to 71 (worst) based on physiologic variables within 24 hours of ICU admission, age and chronic comorbidities (26).

^hThis organ dysfunction score is recorded daily in the ICU and ranges from 0 (best) to 24 (worst) based on six major organ systems (27).

Table 2

Factors Associated with Depression Score during Early Recovery from Acute Lung Injury

Factor ^a	Increase (95% CI) in Depression Score ^b			
	Univariable	P value	Multivariable	P value
BMI >40 kg/m ²	3.5 (1.0, 6.1)	0.007	2.6 (0.2, 5.0)	0.03
Education ≤12 years	2.1 (0.6, 3.6)	0.006	1.2 (-0.3, 2.6)	0.11
Pre-admission depression/anxiety ^c	3.0 (1.4, 4.7)	<0.001	2.0 (0.5, 3.5)	0.007
Admitted to surgical ICU	1.9 (-0.2, 3.9)	0.07	0.2 (-1.8, 2.3)	0.80
Steroid dose ≤50mg prednisone per day	1.6 (-0.4, 3.6)	0.10	1.2 (-0.6, 2.9)	0.18
On insulin infusion protocol	1.5 (-0.6, 3.5)	0.15	0.3 (-1.8, 2.5)	0.74
Mean daily minimum glucose in ICU <100 mg/dL	3.1 (1.6-4.6)	<0.001	2.1 (0.6, 3.7)	0.006

CI, confidence interval; BMI, body mass index; ICU, intensive care unit.

^aFactors presented are those variables from Table 1 which were associated (at $p < 0.15$) with mean depression score. Categories (as presented in Table 1) were collapsed to create a binary variable when a factor's association with depression did not vary across the additional categories.

^bMeasured by the 7-item Hospital Anxiety and Depression (HAD) instrument's depression sub-scale, a continuous measure ranging from 0 to 21 with pre-defined thresholds for depression screening of ≥ 8 and ≥ 11 (31). Results are presented as the increase in mean HAD depression score, comparing patients with the factor of interest to those without that factor, using a linear regression model.

^cPer EQ-5D quality of life survey (29) administered retrospectively to patients before hospital discharge.

Table 3

Factors Associated with Positive Depression Screening Test during Early Recovery from Acute Lung Injury

Factor ^a	Relative Risk ^b (95% CI) for Presence of Depression			
	Univariable	P value	Multivariable	P value
BMI >40 kg/m ²	3.4 (2.0, 5.6)	<0.001	3.3 (1.2, 4.2)	0.03
Education ≤12 years	2.6 (1.1, 5.9)	0.01	2.1 (0.7, 4.3)	0.13
Pre-admission depression/anxiety ^c	4.1 (1.6, 10.0)	<0.001	3.9 (1.5, 6.5)	0.005
Mean daily benzodiazepine dose >100mg/day midazolam	2.4 (1.3, 4.4)	0.004	2.4 (1.1, 3.8)	0.03
Mean daily minimum glucose in ICU <100 mg/dL	2.8 (1.5, 5.4)	<0.001	2.6 (1.2, 4.2)	0.02

CI = confidence interval; BMI, body mass index; ICU, intensive care unit.

^a Factors presented are those variables from Table 1 which were associated (at $p < 0.15$) with presence of a positive depression screening test, defined as a score of ≥ 8 on the Hospital Anxiety and Depression (HAD) depression sub-scale. Categories (as presented in Table 1) were collapsed to create a binary variable when a factor's association with depression did not vary across the additional categories.

^b Univariable p-values were calculated using Fisher's exact test. Multivariable relative risks were calculated using the Zhang and Yu (33) correction to odds ratios obtained from a logistic regression model.

^c Per EQ-5D quality of life survey (29) administered retrospectively to patients before hospital discharge.