Observational Study

Stress Hyperglycemia and Mortality in Subjects With Diabetes and Sepsis

Andrea Fabbri, MD1; Giulio Marchesini, MD2; Barbara Benazzi, MD1; Alice Morelli, MD1; Danilo Montesi, PhD3; Cesare Bini, MD4; Stefano Giovanni Rizzo, PhD5

Objectives: Poor glycemic control is associated with mortality in critical patients with diabetes. The aim of the study was to assess the predicting value of stress hyperglycemia in patients with diabetes following hospital admission for sepsis.

Design: Retrospective observational study.

Setting: Adult, emergency department, and critical care in a district hospital.

Patients: In a 10-year retrospective analysis of sepsis-related hospitalizations in the emergency department, we carried out a secondary analysis of 915 patients with diabetes (males, 54.0%) in whom both fasting glucose at entry and glycosylated hemoglobin were available.

Interventions: None.

Measurements and Main Results: Patients' mean age was 79.0 (sd 11.0), glucose at admission was 174.0 mg/dL (74.3 mg/dL), and glycosylated hemoglobin was 7.7% (1.7%). Stress hyperglycemia was defined by the stress hyperglycemia ratio, that is, fasting glucose concentration at admission divided by the estimated average glucose derived from glycosylated hemoglobin. A total of 305 patients died (33.3%) in hospital. Factors associated with in-hospital case fatality rate were tested by multivariable logistic model. Ten variables predicting outcomes in the general population were confirmed in the presence of diabetes (male sex, older age, number of organ dysfunction diagnoses, in particular cardiovascular dysfunction, infection/parasitic, circulatory, respiratory, digestive diseases diagnosis, and Charlson Comorbidity Index). In addition, also glycemic control (glycosylated hemoglobin: odds ratio, 1.17; 95% CI, 1.15–1.40) and stress hyperglycemia (stress hyperglycemia ratio: 5.25; 3.62–7.63) were significant case fatality rate predictors. High stress hyperglycemia ratio (≥ 1.14) significantly increased the discriminant capacity (area under the receiver operating characteristic curve, 0.864; se, 0.013; p < 0.001).

Conclusions: Stress hyperglycemia, even in the presence of diabetes, is predictive of mortality following admission for sepsis. Stress hyperglycemia ratio may be used to refine prediction of an unfavorable outcome.

Key Words: diabetes; emergency department; mortality; sepsis; stress hyperglycemia ratio

The high mortality rate for sepsis in the elderly population is fueled by several conditions, including multiple comorbidities, frailty, and repeated or prolonged hospitalizations (1, 2). In a large dataset covering all adult sepsis-related hospitalizations in an Italian District hospital in the period 2009–2016, diabetes was selected among variables able to predict mortality with good accuracy (3). Diabetes was very common in this frail and elderly population, accounting for nearly 30% of total cases (3).

The in-hospital mortality risk associated with diabetes in the elderly extends from sepsis (4) to comorbid conditions and cardiovascular risk (5), to drug-related hypoglycemia (6), and all factors fueled by poor glycemic control (7, 8). In the absence of diabetes, hyperglycemia at admission—stress-induced hyperglycemia, acute response to stress (9, 10)—may be even more ominous (11), increasing the risk of complications (12) and mortality (13).

The definition of stress hyperglycemia is a matter of discussion. Recently, Roberts et al (14) proposed relative hyperglycemia (also named stress hyperglycemia ratio [SHR]) as a tool to detect stress-induced hyperglycemia. SHR is defined by the ratio of admission glucose to the estimated average glucose derived from glycated hemoglobin [HbA1c]. As such, SHR, controlling for background glycemic control, proved valid to detect an abnormal response also
in the presence of diabetes. The marker has been shown to be a better correlate of critical illness than absolute hyperglycemia (14), predicting negative outcomes in the elderly in several recent studies (12, 15, 16), particularly in the surgical setting (17–19).

We performed a specific analysis on predictors of case fatality rate (CFR) in the cohort of subjects with diabetes enrolled in our district hospital database on sepsis-associated admissions (3). The aim of the study was to verify if relative hyperglycemia, measured by SHR also drives in-hospital CFR in this specific setting.

MATERIALS AND METHODS

Study Design
In a chart review analysis, we included all adults with sepsis-related hospital admission to the District hospital of Forlì (FC), Italy, from 2009 to 2018, as defined by Singer et al (20). The present cohort is an extension of a previously reported database, updated to 2018 and limited to subjects with a diagnosis of diabetes at entry (3). In emergency department (ED), an electronic warning system is available (systemic inflammatory response syndrome [SIRS]) (21) for the early detection of patients at high risk of sepsis since 2007. The final diagnosis was derived from hospital discharge codes (see below).

Registry Data
The community hospital has a total capacity of 463 beds; during the 10-year study period, over 70,000 cases were hospitalized after ED visits for surgical and medical diseases out of 212,000 admissions. The hospital database is directly connected with the General Registry Office of the District.

Patients
The study included any subject with International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) code for both bacterial and fungal infections and acute organ dysfunction with a code extraction method according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (22, 23). As the study period predated the 2016 definitions (20), sepsis patients were defined by the above criteria, as previously suggested (24, 25). In order to include all cases, we also included cases explicitly coded as severe sepsis (995.92) or septic shock (785.52). This approach was accepted as compatible with the Sepsis-3 (23).

All information extracted by diagnosis codes were matched with data recorded at ED arrival, also in cases without a suspected diagnosis of sepsis at the time of ED presentation.

Data Variables
The variables recorded for analyses included demographic characteristics, main comorbid conditions, the codes of serious infection diagnoses and organ dysfunction diagnoses, and SIRS score greater than or equal to 2 at entry. Data abstractors identified up to five documented diagnoses for each patient by ICD-9-CM codes. For this specific study, three additional parameters were considered: blood glucose, HbA1c, and SHR at admission. SHR was calculated by dividing the fasting glucose concentration by the estimated average glucose derived from HbA1c, assessed by the equation: estimated average glucose (mg/dL) = (28.7 × HbA1c [%])–46.7 (26). Stress hyperglycemia was defined by SHR greater than or equal to 1.14 (16).

In-hospital CFR (i.e., the proportion of all-cause mortality) was verified by a linked local death certificate database and considered for the prognostic model.

Statistical Analysis
The characteristics and outcomes of patients were compared across the 10-year study period (January 2009 to December 2018). Mean value, sd, median, interquartile range, number of cases, and percent with 95% CI were used to describe data distribution. Fisher exact test and Student t test were used to compare categorical and continuous variables between groups.

A multivariable model was developed by stepwise forward analysis of factors significant in univariable analysis and according to clinically relevant predictors. For the model building part of the analysis, the variables were selected on the basis of previous reports and a putative association with main outcome measures, in particular CFR. The full list of covariates can be found in Tables 1 and 2. The following variables were tested as independent parameters, having mortality as outcome: age, sex, SIRS at entry, length of ED stay, diagnosis codes of serious infection and organ dysfunction, and Charlson Comorbidity Index (22), calculated on the basis of the main comorbidities, in particular chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), history of acute heart failure (AHF), dementia, cancer, and HIV infection. Finally, also HbA1c and SHR (dichotomized as below or ≥ 1.14) were included. Data were expressed as odds ratio (OR) and 95% CI.

Colinearity was tested by the variation inflation factor (< 2, not significant). A score for risk of mortality was calculated for each patient on the basis of the coefficients computed by the logistic regression derived from variables entering the stepwise procedure. The accuracy of the scoring system was determined by calculating the area under the receiver operating characteristic (AUROC) curve with se.

The IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY) was used in statistical analyses.

Ethics
The study was approved by the ethical committee of Comitato Etico della Romagna, Romagna, Italy (2299/2019/O/OssN, January 16, 2019). The permission to access the medical records, considering the observational and retrospective nature of the study, was conducted on anonymized records (Privacy guarantor act, GU March 1, 2012, n. 72).

RESULTS
The study population included 915 patients (494 male subjects, 54.0%); their mean age was 79.0 (std, 11.0). The clinical profile of patients in relation to low (< 1.14) or high SHR (≥ 1.14) classes is summarized in Table 1. Main comorbidities were COPD (42.2%), AHF (40.7%), CKD (38.4%), cancer (35.6%), and dementia (32.2%), with high dementia and cancer more represented in the group of patients with high SHR (Table 1).

The most common serious infection diagnoses involved the respiratory system (58.9%), infection/parasitic diseases (42.4%), and the genitourinary tract (26.2%); they all were more represented in subjects with high SHR (Table 2).
The more frequently observed organ/system dysfunction diagnoses involved the pulmonary (51.4%), cardiovascular (34.1), and renal system (22.0%), with cardiovascular dysfunction more represented in subjects with high SHR (56.1% vs 23.1%; OR, 4.24; 95% CI, 3.16–5.79; \(p < 0.001\)) (Table 2).

Charlson Comorbidity Index greater than or equal to 5 was observed in 647 of 915 cases (70.7%); it was recorded in 252 subjects in the high SHR cohort versus 53 among the low SHR cases (82.6% vs 17.4% of total; \(p < 0.001\)).

Among the parameters of glucose metabolism, fasting glucose was 174 mg/dL (74 mg/dL) (mean [sd]), HbA1c was 7.7% (1.7%), and SHR was 1.0 (0.36).

Hospital stay averaged 16 days (20 d) and 15 days (20 d) in subjects with high and low SHR, respectively (\(p = 0.967\)). Overall, 336 patients died in hospital (36.7%) after a mean period of stay of 6 days (13 d) in high SHR and 8 days (18 d) in low SHR (\(p = 0.863\)). Mortality was nearly doubled in subjects (62.8%) with SHR greater or equal to 1.14 compared with subjects with SHR less than 1.14 (37.2%) (OR, 8.71; 95% CI, 6.37–11.91; \(p < 0.001\)).

In the logistic model 10 items, out of the 21 tested, entered as outcome predictors (Table 3), including both HbA1c, a measure of glycemic control, and SHR, that increased the risk of mortality by over five times. Analytical and graphical methods showed that the proportionality assumption of the model was not violated (not
reported in details) and the final model showed an overall accuracy (AUROC curve, 0.864; se, 0.013; \( p < 0.001 \)) (Fig. 1).

In a sensitivity analysis, SHR was also used as continuous variable in the outcome prediction model and similarly entered the regression (OR, 9.52 per one-point increase; 95% CI, 5.60–16.19).

DISCUSSION

In elderly patients with sepsis and diabetes admitted to a general hospital, the study confirms the role of several, previously identified demographic and clinical variables in predicting outcome, but adds both glycemic control and stress hyperglycemia as significant risk factors of poor outcome.

A role of glycemic control was largely expected. Poor control has consistently been reported to increase the risk of infections and cardiovascular outcomes in both type 1 (27) and type 2 (28) diabetes, compared with tight control. The risk might be mediated by the ominous effect of poor glycemic control on immune function and is corrected by intensive insulin administration to target (4). Real world evidence in primary care settings confirmed the risk for sepsis-associated both with diabetes per se and with glycemic control within the diabetes cohort (29), and the same was true in subpopulations with comorbid conditions (30). A recent reappraisal of the problem in over 85,000 patients with diabetes confirmed the long-term risk associated with increasing HbA1c for most outcomes and specifically for infection, with poor control accounting for 21% of attributable fraction of sepsis, 17% of infection-related hospital admission, and 16% of mortality (31). In the presence of sepsis HbA1c was reported as independent predictor of in-hospital mortality (OR, 1.36), together with female sex (OR, 2.24), Acute Physiology and Chronic Health Evaluation (APACHE) II score (OR, 1.08), and Sequential Organ Failure Assessment score (OR, 1.28) (32). The importance of glycated hemoglobin was confirmed in a community-based study from Taiwan (33), in a different hospital-based population, where diabetes-related complications were the most common death risks (34).

The role of stress hyperglycemia is less clearly defined, particularly in the presence of diabetes, also considering the uncertainty of its assessment. In subjects without a diabetes history, the presence of elevated blood glucose during stressful conditions might indicate stress hyperglycemia, but the possibility of recent-onset, unknown diabetes is not excluded. For this reason, Roberts et al (14) proposed SHR, that is, admission glucose divided by the estimated average glucose derived from HbA1c as a tool to detect stress hyperglycemia. By controlling for background blood glucose, SHR was reported to be a better biomarker than absolute hyperglycemia, although the cutoff value to define stress hyperglycemia remains poorly defined. In the original study by Roberts et al (14), a significant increase in mortality was specifically observed in the fourth and fifth SHR quintile, corresponding to average SHR values of 1.14 and 1.38, respectively. In subject with coronary heart disease, Yang et al (35) found an increased mortality risk in the upper SHR quartile of the population; the authors do not provide the exact cut point, but the dichotomized population had a mean value of 0.85 ± 0.15 (quartiles 1–3) versus 1.38 ± 0.32 (quartile 4). Other studies tested SHR as continuous variable (36); in a large

TABLE 3. Predictors of Mortality in Diabetic Subjects Following Diagnosis of Sepsis-Related Hospitalizations by Variables Included in the Logistic Model

| Variables                        | OR (95% CI)   | \( p \)   |
|----------------------------------|--------------|----------|
| Cardiovascular dysfunction       | 4.02 (2.52–6.43) | < 0.001 |
| Circulatory system diseases      | 3.96 (1.89–8.30) | 0.001   |
| Respiratory system diseases      | 3.92 (2.24–6.86) | < 0.001 |
| Digestive system diseases        | 3.27 (1.73–6.20) | < 0.001 |
| Number of organ dysfunction      | 1.64 (1.16–2.32) | 0.006   |
| Age ≥ 80 yr                      | 2.64 (1.74–4.01) | < 0.001 |
| Infectious/parasitic diseases    | 2.93 (1.70–5.05) | < 0.001 |
| Charlson Comorbidity Index       | 1.88 (1.17–3.03) | 0.009   |
| Glycated hemoglobin              | 1.27 (1.15–1.40) | < 0.001 |
| Stress hyperglycemia ratio ≥ 1.14| 5.25 (3.62–7.63) | < 0.001 |

OR = odds ratio.

Variables not included in the model: sex, systemic inflammatory response syndrome score at entry, genitourinary, hematologic, neurologic, other diseases diagnosis, number of serious infections, hepatic, hematoLogic, respiratory, and neurologic dysfunction diagnoses. Data are reported as OR and 95% CIs.

Figure 1. Nonparametric area under the receiver operating characteristic (AUROC) plots of the risk score obtained by logistic regression in identifying case fatality rate of subjects with sepsis and diabetes.
Critical Care Explorations

The study has both strengths and limitations. The main strengths are the large single-center dataset, which guarantees strict adherence to diagnostic criteria and the single laboratory used for blood glucose and HbA1c analysis. Admission blood glucose was considered, not blood glucose in the course of the in-hospital stay, which might vary considerably during hospital stay. The main limitation is the lack of data in subjects without diabetes, where HbA1c was not collected; such records might be used to define the possible role of isolated stress hyperglycemia, as well as to confirm the advantage of SHR over hyperglycemia in detecting the stress-induced glycemic imbalance. An additional limitation, particularly in the elderly and frail population, might be the presence of severe kidney disease with anemia, invalidating the stress-induced glycemic imbalance. An additional limitation is the lack of data in subjects without diabetes, where HbA1c was not collected; such records might be used to define the possible role of isolated stress hyperglycemia, as well as to confirm the advantage of SHR over hyperglycemia in detecting the stress-induced glycemic imbalance. An additional limitation, particularly in the elderly and frail population, might be the presence of severe kidney disease with anemia, invalidating the use of HbA1c as index of glycemic control. This bias would lead to an overestimation of stress hyperglycemia and to false positive cases, likely to dilute the effect of true stress-induced alterations on mortality.

CONCLUSIONS

In summary, our analysis identifies stress-induced hyperglycemia as a relevant prognostic factor also in the presence of diabetes. Mild-to-moderate stress hyperglycemia is considered a protective reaction to providing fuel for the immune system and brain at a time of stress; however, the additional hyperglycemia and insulin resistance it creates may be potentially deleterious (39) directly contributing to adverse outcomes via endothelial dysfunction, increased free radical production (oxidative stress), inflammatory responses, and vascular and immune dysfunction (40). In recent studies, we found that immediate treatment of hyperglycemia by basal-bolus insulin injection, irrespective of the presence of diabetes, reduced adverse events, and septic complications in surgical patients (41). To improve outcomes of critical elderly patients, adequate treatment of hyperglycemia may be systematic implemented also in ED, in keeping with the results observed in ICUs (42).

REFERENCES

1. Hantrakun V, Somayaji R, Teparrukkul P, et al: Clinical epidemiology and outcomes of community acquired infection and sepsis among hospitalized patients in a resource limited setting in Northeast Thailand: A prospective observational study (Ubon-sepsis). PLoS One 2018; 13:e0204509
2. Lee SH, Hsu TC, Lee MG, et al: National Taiwan University Health Economics and Outcome Research Group: Nationwide trend of sepsis: A comparison among octogenarians, elderly, and young adults. Crit Care Med 2018; 46:926–934
3. Fabbri A, Marchesini G, Benazzi B, et al: Old subjects with sepsis in the emergency department: Trend analysis of case fatality rate. BMC Geriatr 2019; 19:372
4. Trevelin SC, Carlos D, Beretta M, et al: Diabetes mellitus and sepsis: A challenging association. Shock 2017; 47:276–287
5. Newman JD, Wilcox T, Smilowitz NR, et al: Influence of diabetes on trends in perioperative cardiovascular events. Diabetes Care 2018; 41:1268–1274
6. Silveira LM, Basile-Filho A, Nicolini EA, et al: Glycaemic variability in patients with severe sepsis or septic shock admitted to an intensive care unit. Intensive Crit Care Nurs 2017; 41:98–103
7. Wang W, Chen W, Liu Y, et al: Blood glucose levels and mortality in patients with sepsis: Dose-response analysis of observational studies. J Intensive Care Med 2019;85506619889322
8. Guo YW, Wu TE, Chen HS: Prognostic factors of mortality among patients with severe hyperglycemia. Am J Manag Care 2015; 21:e9–e22
9. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet 2000; 355:773–778
10. Dungan KM, Braithwaite SS, Preiser JC: Stress hyperglycaemia. Lancet 2009; 373:1798–1807

11. van Vught LA, Holman R, de Jonge E, et al: Diabetes is not associated with increased 90-day mortality risk in critically ill patients with sepsis. Crit Care Med 2017; 45:e1026–e1035

12. Carrasco-Sánchez FJ, Carretero-Gómez J, Gómez-Huelgas R, et al: in: representación del Grupo de Trabajo de Diabetes y Obesidad de la Sociedad Española de Medicina Interna: Stress-induced hyperglycemia on complications in non-critically elderly hospitalized patients. Rev Clin Esp 2018; 218:223–231

13. Chao HY, Liu PH, Lin SC, et al: Association of in-hospital mortality and dysglycemia in septic patients. PLoS One 2017; 12:e0170408

14. Roberts GW, Quinn SJ, Valentine N, et al: Relative hyperglycemia, a marker of critical illness: Introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 2015; 100:4490–4497

15. Rau CS, Wu SC, Chen YC, et al: Stress-induced hyperglycemia in diabetes: A cross-sectional analysis to explore the definition based on the trauma registry data. Int J Environ Res Public Health 2017; 14:1527

16. Di Luzio R, Dusi R, Mazzotti A, et al: Stress hyperglycemia and complications following traumatic injuries in individuals with/without diabetes: The case of orthopedic surgery. Diabetes Metab Syndr Obes 2020; 13:9–17

17. Chrastil J, Anderson MB, Stevens V, et al: Is hemoglobin A1c or perioperative hyperglycemia predictive of periprosthetic joint infection or death following primary total joint arthroplasty? J Arthroplasty 2015; 30:1197–1202

18. Martin ET, Kaye KS, Knott C, et al: Diabetes and risk of surgical site infection: A systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016; 37:88–99

19. Mraovíc B, Subi D, Jacobides C, et al: Perioperative hyperglycemia and postoperative infection after lower limb arthroplasty. J Diabetes Sci Technol 2011; 5:412–418

20. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:801–810

21. Nelson JL, Smith BL, Jared JD, et al: Prospective trial of real-time electronic surveillance to expedite early care of severe sepsis. Ann Emerg Med 2011; 57:500–504

22. Gagne JJ, Glynn RJ, Avorn J, et al: A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011; 64:749–759

23. Shankar-Hari M, Phillips GS, Levy ML, et al: Sepsis Definitions Task Force: Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:775–787

24. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303–1310

25. Iwashyna TJ, Odden A, Rohde J, et al: Identifying patients with severe sepsis using administrative claims: Patient-level validation of the Angus implementation of the international consensus conference definition of severe sepsis. Med Care 2014; 52:e39–e43

26. Nathan DM, Kuenen J, Borg R, et al: A1c-Derived Average Glucose Study Group: Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31:1473–1478

27. The Diabetes Control and Complication Trial Research Group: Adverse events and their association with treatment regimens in the diabetes control and complications trial. Diabetes Care 1995; 18:1415–1427

28. Bartelink ML, Hoek L, Freeriks JP, et al: Infections in patients with type 2 diabetes in general practice. Diabetes Res Clin Pract 1998; 40:15–19

29. McKane CK, Marmarelis M, Mendu ML, et al: Diabetes mellitus and community-acquired bloodstream infections in the critically ill. J Crit Care 2014; 29:70–76

30. Williams ME, Lacson E Jr, Teng M, et al: Extremes of glycemic control (HbA1c) increase hospitalization risk in diabetic hemodialysis patients in the USA. Am J Nephrol 2009; 29:54–61

31. Critchley JA, Carey IM, Harris T, et al: Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care 2018; 41:2127–2135

32. Gornik I, Gornik O, Gasparović V: HbA1c is outcome predictor in diabetic patients with sepsis. Diabetes Res Clin Pract 2007; 77:120–125

33. Yo CH, Lee MT, Gi WT, et al: Prognostic determinants of community-acquired bloodstream infection in type 2 diabetic patients in ED. Am J Emerg Med 2014; 32:1450–1454

34. Hsieh MS, Hu SY, How CK, et al: Hospital outcomes and cumulative burden from complications in type 2 diabetic sepsis patients: A cohort study using administrative and hospital-based databases. Ther Adv Endocrinol Metab 2019; 10:204218819875406

35. Yang Y, Kim TH, Yoon KH, et al: The stress hyperglycemia ratio, an index of relative hyperglycemia, as a predictor of clinical outcomes after percutaneous coronary intervention. Int J Cardiol 2017; 241:57–63

36. Lee TF, Drake SM, Roberts GW, et al: Relative hyperglycemia is an independent determinant of in-hospital mortality in patients with critical illness. Crit Care Med 2020; 48:e115–e122

37. Rattanataweeboon P, Vilaiichone W, Vannasaeng S: Stress hyperglycemia in patients with sepsis. J Med Assoc Thai 2009; 92(Suppl 2):S88–S94

38. Dungan KM, Braithwaite SS, Preiser JC: Stress hyperglycaemia. Lancet 2009; 373:1798–1807

39. Umpierrez GE, Kosiborod M: Inpatient dysglycemia and clinical outcomes: Association or causation? Crit Care Med 2014; 42:427–429

40. Di Luzio R, Dusi R, Morigi A, et al: Nurse-managed basal-bolus versus sliding-scale insulin regimen in subjects with hyperglycemia at admission for orthopedic surgery: A propensity score approach. Acta Diabetol 2020 Feb 25; [online ahead of print]

41. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. N Engl J Med 2001; 345:449–461