ORIGINAL ARTICLE

Effect of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients

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OBJECTIVE: **To assess the effect of an intensive glucose management protocol in a heterogeneous population of critically ill adult patients.**

PATIENTS AND METHODS: **This study consisted of 800 consecutive patients admitted after institution of the protocol (treatment group, between February 1, 2003, and January 10, 2004) and 800 patients admitted immediately preceding institution of the protocol (baseline group, between February 23, 2002, and January 31, 2003). The setting was a 14-bed medical-surgical intensive care unit (ICU) in a university-affiliated community teaching hospital. The protocol involved intensive monitoring and treatment to maintain plasma glucose values lower than 140 mg/dL. Continuous intravenous insulin was used if glucose values exceeded 200 mg/dL on 2 successive occasions.**

RESULTS: **The 2 groups of patients were well matched, with similar age, sex, race, prevalence of diabetes mellitus, Acute Physiology and Chronic Health Evaluation II scores, and distribution of diagnoses. After institution of the protocol, the mean glucose value decreased from 152.3 to 130.7 mg/dL (*P*<.001), marked by a 56.3% reduction in the percentage of glucose values of 200 mg/dL or higher, without a significant change in hypoglycemia. The development of new renal insufficiency decreased 75% (*P*=.03), and the number of patients undergoing transfusion of packed red blood cells decreased 18.7% (*P*=.04). Hospital mortality decreased 29.3% (*P*=.002), and length of stay in the ICU decreased 10.8% (*P*=.01).**

CONCLUSION: **The protocol resulted in significantly improved glycemic control and was associated with decreased mortality, organ dysfunction, and length of stay in the ICU in a heterogeneous population of critically ill adult patients. These results support the adoption of this low-cost intervention as a standard of care for critically ill patients.**

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APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; LOS = length of stay; RBC = red blood cells

An increasingly robust body of literature describes adverse clinical outcomes associated with hyperglycemia. Clinical situations in which impaired glycemic control has been associated with worsened outcomes include myocardial infarction and acute coronary syndromes,[1-6] stroke,[7-11] postoperative wound infections,[12-15] and trauma.[16] A recent review of 1826 consecutive patients admitted to a medical-surgical intensive care unit (ICU) showed that hospital mortality was strongly associated with glycemic control during ICU stay.[17] Patients with mean glucose levels between 80 and 99 mg/dL during ICU stay had a 9.6% hospital mortality; this increased to 12.5% among patients with a mean glucose level of 100 to 119 mg/dL and was as high as 42.5% in patients whose mean glucose level exceeded 300 mg/dL.

Data concerning the treatment of hyperglycemia associated with critical illness are limited. Van den Berghe et al[18] treated postoperative patients undergoing mechanical ventilation with an intensive glycemic protocol with the goal of maintenance of euglycemia. This strategy resulted in a 34% reduction in hospital mortality and a 40% to 50% decrease in organ system dysfunction, such as need for renal replacement therapy, blood transfusion requirements, and critical illness polyneuropathy. Furnary et al[19] recently reviewed their experience with the use of continuous intravenous insulin in diabetic patients after cardiac surgery and reported that mortality was less than half of that seen in an earlier series of patients treated with subcutaneous insulin only. To my knowledge, the effect of an intensive glycemic management protocol in a medical-surgical population of critically ill adult patients has not been described previously.

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PATIENTS AND METHODS

The Stamford Hospital is a 305-bed community hospital that serves as a major teaching affiliate of the Columbia University College of Physicians and Surgeons; it maintains freestanding residency programs in internal medicine, family practice, general surgery, and obstetrics-gynecology. The adult ICU has 14 beds. The unit has a "hybrid" configuration, merging characteristics of both "open" and "closed" models. Medical and surgical residents write all orders in the unit; they are supervised closely by the director of critical care and the director of surgery, who complete rounds daily with the medical and surgical house staff, respectively. Any credentialed attending physician can admit a patient to the unit, but appropriate critical care or organ-specific subspecialty consultations are obtained for all patients. Patients are admitted to the ICU with a wide variety of medical and surgical diagnoses. Cardiac surgery

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is not performed at the hospital. A small minority of patients are adolescents. A nurse epidemiologist reviews every chart daily for evidence of infections acquired in the ICU. The hospital's infection control committee then reviews all suspected cases for confirmation.

This study compared the outcomes of 800 patients admitted consecutively to the ICU immediately before institution of the glucose management protocol (February 23, 2002, through January 31, 2003) to those of the first 800 patients admitted after institution of the protocol (February 1, 2003, through January 10, 2004). There were a total of 64 readmissions to the ICU during the same hospitalization among the patients in the baseline group and a total of 51 among the patients in the treatment group. Primary diagnostic category, APACHE II scores,[20] and length of stay (LOS) in the ICU were based on each patient's first admission to the ICU; data regarding glucose values and organ system dysfunction combine all ICU stays.

ICU Databases

A comprehensive database tracks multiple outcomes for all patients admitted to the unit. The director of critical care or his associate updates the core dataset daily, ensuring data accuracy and integrity. These are the only 2 individuals maintaining the database; quality assurance issues, including "scoring" questions, are discussed regularly. The database is linked to other databases within the hospital system, allowing analysis of laboratory data and final discharge status. Data included in this report include age; primary diagnosis assigned at the time of admission to the unit, based in part on the more than 80 diagnoses used by the APACHE III system[21]; LOS in the ICU measured in 0.1-day increments; APACHE II score based on data from the first 24 hours in the ICU; diagnosis of diabetes mellitus at the time of ICU admission; glucose (mg/dL), creatinine (mg/dL), and hemoglobin values during ICU stay; transfusion requirements; and final discharge status.

Glycemic Management Protocol

The glycemic management protocol (Figure 1), written by a multidisciplinary group of physicians and nurses at The Stamford Hospital after review of the medical literature, was incorporated into use on February 1, 2003. The goal of the protocol is to maintain glucose levels lower than 140 mg/dL. Nurses perform intensive monitoring of fingerstick glucose values, initially at an interval of every 3 hours but less frequently if glucose values are stable. If the results of a contemporaneous plasma glucose assay are available, there is no need to obtain fingerstick glucose values. Continuous intravenous insulin is used if the fingerstick glucose value exceeds 200 mg/dL on 2 successive occasions; subcutaneous regular insulin is used for lower glucose levels. Longer-acting insulin products, or oral hypoglycemic agents when appropriate, are used as soon as feasible to minimize abrupt fluctuations in glycemic control. The protocol is nurse driven. Nurses administer insulin without a physician's order based on the parameters of the protocol; if a patient needs a different amount of insulin than the protocol states, a specific order is required.

Glucose Measurements

Plasma glucose measurements were tracked and analyzed using linkages between the core dataset and the laboratory database. All plasma glucose assays were performed using Vitros 950 and Vitros 250 chemistry analyzers (Ortho-Clinical Diagnostics, a division of Johnson & Johnson, Raritan, NJ).

Statistical Analyses

Statistical analysis was performed using the SPSS 11.0 statistical package. Glucose values, age, LOS, and APACHE II scores were expressed as median and interquartile range. Length of stay in the ICU was measured in 0.1-day increments; therefore, the shortest LOS abstracted from the database was 0.0 days (total LOS in the ICU, <1 hour). Comparisons of age, LOS, and APACHE II scores between patients in the consecutive series of historical controls (baseline group) and patients who underwent the treatment protocol (treatment group) were performed using the Wilcoxon signed rank test. The χ^2 statistic was used to assess differences between the baseline group and treatment group regarding sex, race, percentage of patients with diabetes, percentage of medical vs surgical services, percentage of patients requiring red blood cell (RBC) transfusions, and mortality rates in the ICU and hospital. The Fisher exact test was used to assess differences between the baseline group and the treatment group in the development of new renal insufficiency during ICU stay. Statistical significance was defined as $P<.05$. All results were 2-tailed.

The Stamford Hospital Institutional Review Board approved this study.

RESULTS

Comparison of Baseline Group and Treatment Group

Selected characteristics of the baseline group and treatment group are reported in Table 1. There was no significant difference between the 2 groups in age, sex, race, percentage of patients with diabetes, severity of illness at ICU admission as defined by the APACHE II score, or percentage of patients admitted to the medical vs surgical service. No significant difference was noted between the baseline group and treatment group regarding the number of pa-

ICU PROTOCOL FOR GLYCEMIC MANAGEMENT

Approved by the ICU Committee 2/11/03
Last modified by the ICU Multidisciplinary Committee 9/26/03

Rationale

Hyperglycemia is strongly associated with increased hospital mortality as well as organ system dysfunction among critically ill patients.

MD Signature_____

Date_____

Goal

The goal of this protocol is to maintain serum glucose <140 mg/dl.

Monitoring

Glucose levels will be evaluated ***by blood testing or fingerstick testing***, using the following schedules:

Diet	Frequency of monitoring
NPO	Q6 hours: 6AM, noon, 6PM, midnight
PO diet	1 hour AC and QHS
Tube feedings, TPN	Q6 hours: 6AM, noon, 6PM, midnight

For most patients, the 6AM glucose evaluation will be obtained from the morning BMP. If glucose <140 for two consecutive days without treatment, glucose levels can be checked Q12 hours (6AM, 6PM)

Treatment of hyperglycemia

Glucose value	Action (subcutaneous insulin dose)
<140	No treatment
140-169	3 units Regular insulin; Recheck glucose value in 3 hours
170-199	4 units Regular insulin; Recheck glucose value in 3 hours
200-249	6 units Regular insulin; Recheck glucose value in 3 hours
250-299	8 units Regular insulin; Recheck glucose value in 3 hours
300+	10 units Regular insulin; Recheck glucose value in 3 hours

- ***If glucose value exceeds 200 on two successive measurements, a continuous insulin infusion will be initiated. Hourly FSG or blood glucose measurements will be obtained in all patients receiving insulin infusions. The sliding scale noted above is a guideline; it can be modified if the patient requires more or less intensive therapy.***

Management of insulin infusion

1. Initial infusion rate

Glucose value	Insulin dose
200-249	4 units/hour
250-299	6 units/hour
300-399	8 units/hour
400+	10 units/hour

2. Subsequent management, based on hourly glucose checks

Glucose value	Insulin dose
<140	Stop infusion or continue low dose to avoid "rebound"
140-169	2 unit/hour
170-199	3 units/hour
200-249	4 units/hour
250-299	6 units/hour
300-399	8 units/hour
400+	10 units/hour

Important points

- All patients receiving continuous insulin must receive a continuous source of glucose, either via IV (D5W or TPN), or enteral feeds.
- The insulin infusion is discontinued if the patient has to leave the ICU for a diagnostic test as well as upon discharge from the ICU

If this treatment plan does not lead to a decrease in the patient's glucose values, contact the house officer.

FIGURE 1. Glucose management protocol. AC = before meals; BMP = basic metabolic profile; FSG = fingerstick glucose; ICU = intensive care unit; IV = intravenous; NPO = nothing by mouth; PO = by mouth; QHS = every night; TPN = total parenteral nutrition.

tients, age, or APACHE II scores in each of the major diagnostic categories (Table 2).

Effect of the Protocol on Glycemic Control

The glycemic management protocol led to significantly improved glucose levels without a significant increase in hypoglycemia. The distribution of glucose values for the baseline group and treatment group is shown in Figure 2. The mean (SD) and median (interquartile range) glucose levels for the baseline group were 152.3 (93.4) mg/dL and 130.7 (107-172) mg/dL, respectively. These decreased to 130.7 (55.1) mg/dL and 119 (99-147) mg/dL in the treatment group ($P<.001$). After institution of the protocol, there was a 56.3% decrease in the percentage of glucose values of 200 mg/dL or higher, from 16.2% to 7.1% ($P<.001$). The percentage of patients with marked hypoglycemia, defined as glucose values lower than 40 mg/dL, was 0.35% during the baseline period and 0.34% during the treatment period ($P=.89$). The percentage of patients with mild hypoglycemia, defined as glucose values of 40 to 59 mg/dL, increased from 0.54% to 1.02% ($P=.02$ by the χ^2 test). No associated adverse clinical sequelae occurred.

Organ System Dysfunction

The number of patients with new renal dysfunction after ICU admission, defined as initial serum creatinine level of 1.5 mg/dL or lower with maximum serum creatinine level of 2.5 mg/dL or higher or initial serum creatinine level lower than 1.5 mg/dL with maximum serum creatinine level 2 or more times the initial value, decreased from 12 to 3 after institution of the protocol ($P=.03$ by Fisher exact test).

The number of patients requiring transfusions of packed RBCs decreased after institution of the protocol. Excluding patients admitted to the ICU with a primary diagnosis of acute upper or lower gastrointestinal tract bleeding (50 in the baseline group and 44 in the treatment group), 25.2% of the baseline group and 20.5% of the treatment group (an 18.7% reduction) ($P=.04$) received a mean (SD) of 3.79 (3.32) and 3.30 (3.13) units of packed RBCs ($P=.17$), respectively. The lowest hemoglobin concentration among the patients undergoing packed RBC transfusions did not change significantly (median [interquartile range]: baseline group, 8.0 [7.2-8.8]; treatment group, 7.9 [6.9-9.5]; $P=.95$), suggesting that the "trigger" for transfusion did not change between the 2 periods.

The number of patients with infections acquired in the ICU was low during the baseline period and did not change significantly during the protocol period (Table 3). Central lines impregnated with chlorhexidine and silver sulfadiazine were in use in the ICU since 2001. Femoral line insertions were limited to 3 days, and a policy requiring draping, gowning, and masking for line insertions was in place during both periods. The nurse epidemiologist who reviewed every patient record for evidence of ICU-acquired infections prospectively has been performing this task, using the same criteria, since 1996.

TABLE 1. **Demographic Data for Baseline and Treatment Group***

Characteristic	Baseline	Treatment	*P* value
Male	437 (54.6)	423 (52.9)	.52†
White	601 (75.1)	597 (74.6)	.86†
Black	130 (16.3)	123 (15.4)	.68†
Other	69 (8.6)	80 (10.0)	.39†
Median age (y) (interquartile range)	70 (53-80)	69 (52-79)	.21‡
Median APACHE II score (interquartile range)	16 (10-23)	15 (10-22)	.11‡
Diabetic	131 (16.4)	145 (18.1)	.39†
Medical service	502 (62.8)	525 (65.6)	.25†

*Values represent number (percentage) unless indicated otherwise. APACHE = Acute Physiology and Chronic Health Evaluation.
†χ^2 test.
‡Wilcoxon signed rank test.

TABLE 2. **Distribution of Diagnoses Between Baseline and Treatment Group***

Diagnostic category†	Baseline			Treatment		
	No. (%) of patients	Age (y)	APACHE II score	No. (%) of patients	Age (y)	APACHE II score
Cardiac	143 (17.9)	74 (61-84)	17 (11-24)	141 (17.6)	74 (58-81)	16 (11-23)
Respiratory	97 (12.1)	73 (61-81)	21 (17-27)	102 (12.8)	74 (60-80)	20 (16-25)
Other medical	86 (10.8)	62 (50-80)	16 (12-22)	93 (11.6)	58 (45-77)	15 (11-22)
Septic shock‡	34 (4.3)	73 (54-83)	28 (20-36)	41 (5.1)	72 (64-82)	25 (21-32)
Neurologic	99 (12.4)	64 (49-77)	12 (8-21)	113 (14.1)	58 (45-72)	11 (7-16)
Trauma	48 (6.0)	42 (26-60)	12 (8-18)	38 (4.8)	35 (24-55)	8 (3-17)
General surgical	143 (17.9)	71 (57-78)	14 (9-18)	122 (15.3)	72 (61-80)	13 (9-16)

*Age and Acute Physiology and Chronic Health Evaluation (APACHE) II scores expressed as median (interquartile range).
†Primary admitting diagnosis assigned by the director of critical care at the time of admission; diagnostic categories are mutually exclusive.
‡Defined by criteria established by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine.[22]

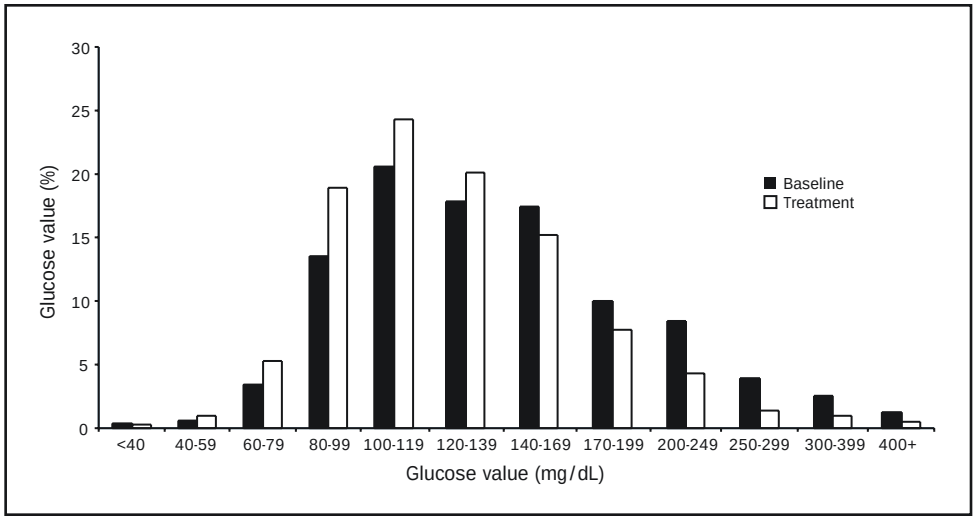

FIGURE 2. Effect of protocol on glucose values.

Mortality and LOS in the ICU

Hospital mortality decreased 29.3% during the protocol period (167 patients [20.9%] in the baseline group died vs 118 [14.8%] in the treatment group; *P*=.002). A decrease in mortality was noted among most of the subpopulations, most striking among the patients with septic shock or a neurologic or surgical diagnosis (Table 4). Mortality differences grouped by APACHE II scores are shown in Table 5. The improved survival among patients undergoing the glycemic management protocol was notable regardless of acuity of illness, except among those most profoundly ill at ICU admission with APACHE II scores of 35 or higher.

Mean (SD) LOS in the ICU decreased from 3.58 (4.80) days in the baseline group to 3.19 (4.79) days in the treatment group (*P*=.11). Median (interquartile range) LOS in the ICU decreased from 1.9 (1.0-3.9) days in the baseline group to 1.6 (0.9-3.3) days in the treatment group (a 10.8% reduction) (*P*=.01).

Comparison of Results to a Second Baseline Period and Temporal Trends in Glycemic Management

To exclude the possibility that the decreased mortality rate of patients in the treatment group was due to a temporal trend in the improvement of care in the ICU within the hospital in general, an additional group of 800 patients, admitted to the ICU just before the patients in the baseline group, was abstracted from the database. The APACHE II score (median, 15; interquartile range, 10-22) and age (median, 68 years; interquartile range, 53-79 years) of the patients were not significantly different from those of the baseline or treatment group. The hospital mortality of this group was 18.9% (*P*=.35 compared with the baseline group). The mean (SD) LOS in the ICU was 3.43 (5.20) days (*P*=.55 compared with the baseline group), and the median (interquartile range) LOS in the ICU was 1.9 (1.0-3.4) days (*P*=.25 compared with the baseline group).

The stability of glucose control in the ICU during the 3 years before institution of the intensive glycemic management protocol is shown in Table 6. There was no significant difference in the mean glucose value or the percentage of glucose values of 200 mg/dL or higher during this period. The mean value and percentage of glucose values of 200 mg/dL or higher decreased substantially after institution of the protocol (*P*<.001 for all comparisons).

Effect of the Protocol on Staffing Requirements in the ICU

There was no significant change in staffing requirements in the ICU due to the increased work burden imposed by the protocol. Between February 1, 2002, and January 31, 2003, there were 49,105 paid hours for registered nurses (11.12 hours per patient-day). Between February 1, 2003, and January 31, 2004, there were 46,867 paid hours for registered nurses (11.19 hours per patient-day).

DISCUSSION

The salient finding of this study is that a protocol designed to maintain blood glucose levels lower than 140 mg/dL was associated with a 29.3% decrease in mortality among a heterogeneous population of critically ill adult patients. The principal strengths of this study include the large number of patients evaluated, the consistent find-

ings among the subpopulations analyzed, and the generalizability of the results.

The main limitation of the study is its use of historical controls in a nonrandomized design. Treatment of hyperglycemia was not standardized in the baseline period, and the caloric intake or frequency of blood glucose determinations was not standardized in either period. Nevertheless, equal groups of patients admitted consecutively to the ICU before and after institution of the protocol were compared, and the groups were evenly matched regarding age, sex, race, diagnostic category, prevalence of diabetes, and acuity of illness based on APACHE II scores. There were no major changes in the process of care in the ICU from the 11 months of the baseline period to the 11 months of the intervention period. Specifically, 2 recent advances in critical care, the use of drotrecogin alfa (activated) in patients with severe sepsis[23] and low tidal volume ventilation in patients with the acute respiratory distress syndrome,[24] were used as indicated in both patient populations. Moreover, there was no change in the trigger for transfusion of packed RBCs during this period. Finally, a second baseline group, consisting of 800 patients admitted to the ICU just before the baseline group, was identified. The APACHE II scores, age, hospital mortality rate, and LOS in the ICU of this second group were not significantly different than those of the baseline group, suggesting that an overall temporal trend in improvement in ICU care at the hospital was not the cause of the decreased mortality during the protocol period.

Care at The Stamford Hospital ICU is highly protocol driven. Management protocols guide many routine aspects of care, including enteral nutrition, deep venous thrombosis prophylaxis, stress peptic ulcer prophylaxis, weaning from mechanical ventilation, and sedation of patients undergoing mechanical ventilation. The close supervision of the medical and surgical house staff, who write all orders in the unit, allows a high degree of control over the quality and consistency of care and ensures compliance with the numerous patient care protocols. Moreover, ancillary staffing ratios were unchanged during the baseline and intervention periods. The standard of care required a nurse-patient ratio of 2:1, and the unit was staffed by full-time respiratory therapists throughout the study. Finally, there was no change in the number of paid hours for registered nurses during the treatment period compared with the baseline period.

The glycemic goals of the protocol used in this study contribute to its applicability to other institutions. The threshold of 140 mg/dL was chosen in part for practical reasons. The nurses and physicians who developed the glycemic management protocol concluded that this level was achievable without increasing the risk of treatment-related severe hypoglycemia. In fact, the percentage of glucose values lower than 40 mg/dL was 0.35% during the baseline period and 0.34% during the intervention period (*P*=.89). Moreover, the amount of extra work imposed on the nursing staff by the protocol was an important factor when considering its promulgation and likelihood of success. The standard of care in the ICU before institution of the protocol, likely similar to that in most ICUs then and now, tolerated moderate levels of hyperglycemia. Typically, insulin would not be administered unless blood glucose values exceeded 200 mg/dL. The new protocol mandated much more intensive monitoring of fingerstick glucose levels and treatment with insulin when fingerstick glucose levels were 140 mg/dL or higher. Continuous intravenous insulin, requiring even more frequent fingerstick glucose evaluations, was used when fingerstick glucose levels exceeded 200 mg/dL on 2 successive occasions. The protocol was nurse driven, requiring explicit orders only when variances to the protocol occurred. Therefore, the success of the protocol depended primarily on the nursing staff's willingness to perform the extra work necessary to achieve its goals. This success was manifested by a 42.4% increase in the percentage of plasma glucose values between 60 and 99 mg/dL (from 17.0% to 24.2%) and a 56.3% decrease in the percentage of blood glucose values of 200 mg/dL or higher (from 16.2% to 7.1%) during the 2 periods.

The beneficial effect on mortality extended through the entire range of severity of illness up to the most profound and catastrophic. There was no improvement in mortality among patients with APACHE II scores of 35 or higher. In contrast, mortality decreased 73.8% among patients with the lowest acuity of illness at presentation (APACHE II score <15), 30.2% among patients with an APACHE II score of 15 to 24, and 29.4% among severely ill patients with APACHE II scores of 25 to 34. Although this study was not powered adequately to allow robust subgroup analysis, mortality decreased among patients in most of the separate diagnostic categories. This finding was most prominent among the neurologic patients, who had a decrease in mortality from 21.0% to 8.5% (*P*=.007), and the

TABLE 3. **Infections Acquired in the Intensive Care Unit Between Baseline and Treatment Group**

Type of infection	Baseline	Treatment
Ventilator-associated pneumonia	6	3
Non–ventilator-associated pneumonia	1	6
Urinary tract infection	10	9
Surgical wound infection	5	2
Methicillin-resistant *Staphylococcus aureus*	2	0
Clostridium difficile	1	1
Central line infection	2	0
Vancomycin-resistant enterococcus	0	0
Total	27	21

TABLE 4. **Mortality of Patients in the Baseline and Treatment Group***

	Baseline		Treatment			*P* value†	
Patient subgroup	APACHE II score	Hospital mortality (%)	APACHE II score	Hospital mortality (%)	% Decrease (increase) in mortality	APACHE II score	Hospital mortality (%)
All patients	16 (10-23)	20.9	15 (10-22)	14.8	29.3	.11	.002
Cardiac	17 (11-24)	20.1	17 (11-23)	15.5	22.9	.86	.48
Respiratory	21 (17-26)	26.1	20 (16-26)	21.6	17.2	.50	.51
Other medical	16 (12-22)	9.7	15 (11-23)	11.1	(14.4)	.94	.90
Septic shock	28 (22-36)	60.4	25 (21-32)	33.3	44.9	.20	.02
Neurologic	12 (8-21)	21.0	11 (7-17)	8.5	59.5	.13	.007
Trauma	13 (8-23)	17.8	8 (4-19)	19.5	(9.6)	.01	.81
General surgical	12 (9-18)	16.8	12 (9-16)	8.6	48.8	.77	.04

*Acute Physiology and Chronic Health Evaluation (APACHE) scores expressed as median (interquartile range).
†χ^2 analysis.

patients with septic shock, who had a decrease in mortality from 60.4% to 33.3% (*P*=.02) during the study.

A growing body of literature describes the adverse consequences of hyperglycemia in a variety of different clinical contexts. Hyperglycemia impacts the prognosis of both medical and surgical cardiac patients. Hyperglycemia at admission was correlated with increased mortality among patients with acute coronary syndrome[4] and those with myocardial infarction.[1] An increased risk of wound infections after cardiac and general surgery was noted by several different investigators.[12-15] Hyperglycemia was associated with worsened outcomes among patients presenting with acute ischemic stroke[7,10] and after treatment with recombinant tissue-type plasminogen activator.[11]

A recent review of 1826 patients found a striking relationship between increasing glucose levels during ICU stay and increasing hospital mortality among a heterogeneous population of critically ill patients.[17] The lowest mortality was observed in patients with mean glucose levels of 80 to 99 mg/dL. Nonsurvivors had higher mean glucose levels than did survivors, and this observation extended from the entire population to each of the subpopulations analyzed.

Relatively few studies have investigated the effect of strict glycemic control on outcomes of acutely ill patients. Rates of sternal wound infection in a large cohort of diabetic patients who underwent cardiac surgery were reduced with use of continuous intravenous insulin rather than "sliding scale" subcutaneous administration of insulin that resulted in improved glycemic control.[19] The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction Study Group reported that intensive glycemic management using continuous intravenous insulin followed by intensive subcutaneous administration of insulin was associated with a 28% reduction in mortality among 620 diabetic patients with acute myocardial infarction.[5]

Van den Berghe et al[18] used an intensive protocol in a population of postoperative cardiothoracic patients undergoing mechanical ventilation with the goal of maintaining euglycemia (blood glucose level, ≤110 mg/dL). Hospital mortality decreased by 34% in the intensively treated group, and bacteremia, renal failure, RBC transfusions, and critical illness polyneuropathy also decreased. The current study suggests that the findings of Van den Berghe et al in a narrow population of postoperative patients may extend to a heterogeneous population of critically ill adult patients treated in a medical-surgical ICU of a university-affiliated community hospital.

The patients in the intervention group of the current study also experienced improvements beyond the mortality benefit. The number of patients who developed new renal insufficiency after admission to the ICU (defined as initial serum creatinine level ≤1.5 mg/dL with maximum serum creatinine level ≥2.5 mg/dL or initial serum creatinine level

TABLE 5. **Mortality Related to APACHE II Scores***

	Baseline		Treatment			
APACHE II score	No. of patients	Mortality (%)	No. of patients	Mortality (%)	% Decrease (increase) in mortality	*P* value
0-14	356	4.2	379	1.1	73.8	.01
15-24	276	19.2	268	13.4	30.2	.09
25-34	120	51.7	107	36.5	29.4	.03
35+	48	77.1	46	84.8	(10.0)	.49

*APACHE = Acute Physiology and Chronic Health Evaluation.

>1.5 mg/dL with maximum serum creatinine level 2 or more times the initial value) decreased from 12 during the baseline period to 3 during the intervention period (P=.03 by Fisher exact test). There was also a decrease in the number of patients receiving transfusions of packed RBCs (P=.04) with no evidence for a change in the threshold trigger for transfusion. The number of patients acquiring infections after admission to the ICU did not change significantly during this study, a result that differs from that of the study by Van den Berghe et al. One possible explanation is the fact that the infection rate at The Stamford Hospital ICU is already low. The rate of central line infection has been close to 0% for several years because of the use of antibiotic-impregnated catheters and policies regarding universal gloving, gowning, and draping. The ventilator-associated pneumonia rate is also low, perhaps related to the standard application of multiple protocols and patient care guidelines in the ICU, such as elevation of the head of the bed, universal gloving, and closed catheter suctioning systems. Finally, the LOS in the ICU was short (baseline group: median 1.9 days, mean 3.58 days; treatment group: median 1.6 days, mean 3.19 days).

What are some of the reasons improved glycemic control is associated with improved outcomes in several clinical contexts? Coursin and Murray[25] summarized several leading hypotheses in a recent editorial, including elimination of glucose-induced osmotic diuresis, maintenance of macrophage and neutrophil function, enhancement of erythropoiesis, reduction of cholestasis, direct anabolic effect of insulin on respiratory muscles, and reduction of hyperglycemic injury of neuronal axons. The potential anti-inflammatory effects of insulin have been evaluated by several investigators.[26-28] Finally, there is uncertainty whether it is the actual insulin dose received per se or the degree of euglycemia achieved that is responsible for the beneficial effects of intensive glycemic management. Van den Berghe et al[29] performed a multivariate logistic regression analysis on the data derived from their series of postoperative patients undergoing mechanical ventilation and determined that the degree of glycemic control, rather than the quantity of insulin administered, was associated with the decrease in mortality and organ system dysfunction. Finney et al[30] reported that insulin administration was positively correlated with mortality regardless of the prevailing blood glucose level, suggesting that glycemic control was the responsible factor among a cohort of 523 patients predominantly undergoing cardiac surgery. The issue of whether increased insulin administration or glycemic control per se is responsible for Van den Berghe's highly positive outcomes has been hotly debated.[31-33] The current study was not designed to shed light on the mechanisms of improved outcomes related to intensive glycemic management; investigations are needed to elucidate these mechanisms.

TABLE 6. **Temporal Trends in Glucose Control**

One-year period beginning	Mean (SD) glucose (mg/dL)	% Glucose values ≥200 mg/dL
February 2000	154.7 (85.9)	18.8
February 2001	152.9 (78.8)	19.1
February 2002	152.5 (93.2)	16.4
February 2003	130.7 (55.1)	7.3

CONCLUSION

This study evaluated the effects of an intensive glycemic management protocol instituted in a medical-surgical ICU of a university-affiliated community hospital. The reduction in the mortality rate during the intervention period was 29.3%, associated with a decrease in the LOS in the ICU and a reduction in the development of new renal insufficiency and packed RBC transfusion requirements. The setting and the reasonable goal of the protocol—maintenance of blood glucose levels lower than 140 mg/dL—make the findings generalizable. Nevertheless, the use of consecutive historical controls compared with consecutive protocol patients limits the strength of the conclusions that can be drawn from these data. Well-designed prospective, randomized controlled trials of intensive glycemic management in medical and general surgical populations are needed to confirm the adoption of this low-cost intervention as a standard of care for the treatment of critically ill patients.

ADDENDUM

Since completion of the manuscript, an additional 300 patients have been admitted to the ICU and monitored to hospital discharge. The median (interquartile range) APACHE II score of these patients was 16 (11-23), and the hospital mortality rate was 14.3% (unpublished data).

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REFERENCES

1. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL, ICONS Investigators. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol.* 2002;40:1748-1754.

2. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773-778.

3. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated

patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation*. 1999;99:2626-2632.

4. Foo K, Cooper J, Deaner A, et al. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart*. 2003;89:512-516.

5. Malmberg K, DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ*. 1997;314:1512-1515.

6. Sala J, Masia R, Gonzalez de Molina FJ, et al, REGICOR Investigators. Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission. *J Epidemiol Community Health*. 2002;56: 707-712.

7. Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 2002;59:67-71.

8. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426-2432.

9. Kagansky N, Levy S, Knobler H. The role of hyperglycemia in acute stroke. *Arch Neurol*. 2001;58:1209-1212.

10. Parsons MW, Barber PA, Desmond PM, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 2002;52:20-28.

11. Bruno A, Levine SR, Frankel MR, et al, NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59:669-674.

12. Estrada CA, Young JA, Nifong LW, Chitwood WR Jr. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg*. 2003;75:1392-1399.

13. Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. *Endocr J*. 2002;49:531-537.

14. Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol*. 2001;22:607-612.

15. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care*. 1999;22:1408-1414.

16. Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. *J Trauma*. 2003;55:33-38.

17. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78:1471-1478.

18. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.

19. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:1007-1021.

20. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-829.

21. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100:1619-1636.

22. Bone RC, Balk RA, Cerra FB, et al, American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992; 101:1644-1655.

23. Bernard GR, Vincent JL, Laterre PF, et al, Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-709.

24. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301-1308.

25. Coursin DB, Murray MJ. How sweet is euglycemia in critically ill patients? [editorial]. *Mayo Clin Proc*. 2003;78:1460-1462.

26. Das UN. Is insulin an antiinflammatory molecule? *Nutrition*. 2001;17: 409-413.

27. Das UN. Is insulin an endogenous cardioprotector? *Crit Care*. 2002;6: 389-393.

28. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab*. 2003;88:1082-1088.

29. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359-366.

30. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290:2041-2047.

31. Annane D, Melchior JC. Hormone replacement therapy for the critically ill [editorial]. *Crit Care Med*. 2003;31:634-635.

32. Van den Berghe G, Bouillon R. Optimal control of glycemia among critically ill patients [letter]. *JAMA*. 2004;291:1198-1199.

33. Finney SJ, Evans TW. Optimal control of glycemia among critically ill patients [reply]. *JAMA*. 2004;291:1199.