Intensive insulin therapy confers a similar survival benefit in the burn intensive care unit to the surgical intensive care unit

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Background. *In contrast to the benefits of intensive insulin therapy (IIT) in the surgical intensive care unit (SICU), its benefits in the burn ICU (BICU) remain unclear. Furthermore, IIT and tight glycemic control has received little attention in elderly ICU patients.*

Methods. *We evaluated the normalization of blood glucose level with IIT in BICU and SICU patients. From October 2006 to July 2007, 970 patients were admitted to our BICU and our SICU. A total of 79 of these patients met criteria for initiation of IIT, 37 of who required IIT for at least 72 hours. Data were analyzed to determine if tight glycemic control (blood glucose ≤150 mg/dL by day 3) is associated with reduced morbidity and mortality.*

Results. *Tight control was better achieved in SICU patients (45%) than in BICU patients (33%). Daily insulin requirements were approximately 2-fold greater in SICU patients compared with BICU patients (P < .05). Tight control in both SICU and BICU patients was associated with a decreased incidence of sepsis compared with poor glycemic control (10% vs 58% and 60% vs 70%, respectively) and a decreased mortality rate (0 vs 58% and 20% vs 50%; SICU vs BICU, respectively). The percentage of total body surface area burned in BICU patients was 10% and 45% in the ≤150 and >150 mg/dL groups. Mortality rate in the poor control group was >10-fold greater than that of the tight control group; for patients ≥65 years of age, mortality was nearly double than that of patients <65 years of age. The greatest mortality rate (62%) was seen in patients >65 years of age with poor control.*

Conclusion. *Tight control with IIT is associated with an increased survival rate in both BICU and SICU patients. Age is associated with survival, with patients older than 65 years of age having the greatest mortality rate. (Surgery 2009;146:922-30.)*

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Intensive treatment of hyperglycemia in critically ill patients has substantial positive outcomes.[1-3] In 2001, Van den Berghe et al[1] showed that maintenance of euglycemia with intensive insulin therapy (IIT) in a mixed-service surgical intensive care unit (SICU) was associated with reduced mortality, morbidity, and duration of stay in critically ill surgical patients, largely due to a striking reduction in infection.[1]

Currently, the use of IIT to achieve tight glycemic control is becoming a standard practice in many medical facilities. However, achievement of tight glycemic control to levels reported by Van den Berghe[1] is extremely difficult and costly (both physiologically and monetarily), and seldom achieved. In fact, a recent metaanalysis[4] reports that Van den Berghe et al's study is an outlier. Nevertheless, it is still not clear whether tight control should be the goal and whether, or to what degree, it is beneficial.[5]

Most recently, the results of the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR)

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study were published.[6] This large randomized trial reported that, in an intensive glucose control group (target level: range, 81–108 mg/dL), mortality among patients in the intensive care unit (ICU) was increased compared to a conventional glucose control group (target level, ≤180 mg/dL). In the intensive glucose control group, severe hypoglycemia (blood glucose ≤40 mg/dl) occurred in 6.8% of the patients and only 0.5% of the patients in the conventional control group.

The American Diabetes Association and the American Association of Clinical Endocrinologist responded to this report by suggesting that, until more data are available, it is prudent to treat critically ill patients less intensively rather than attempt to achieve blood glucose levels in the range of 80 to 108 mg/dL.[7] Similarly, in response to the NICE-SUGAR report, the Endocrine Society has suggested that the target value in the ICU should be between 144 and 180 mg/dL.[8]

In October 2006, the Johns Hopkins Bayview Medical Center Surgical and Burn Intensive Care Units (SICU and BICU) instituted an intensive insulin infusion protocol (IIT) based upon the Yale protocol.[3] Since that time, the IIT protocol has been used in hyperglycemic critically ill adult patients in the mixed-service surgical intensive care unit (SICU) and burn intensive care unit (BICU) with an anticipated duration of stay greater than 24 hours. The protocol involves the use of continuous intravenous (IV) insulin accompanied by hourly monitoring until blood glucose levels and insulin demand have stabilized. As a part of the protocol, glucose levels and insulin titration are reviewed for each patient to assess the protocol's effectiveness.

Although the benefit of tight glycemic control obtained by IIT has been demonstrated in the SICU population,[1-3] the benefit of IIT in the BICU patient population remains unclear. The response to burn injury is similar to the hyperglycemic stress response induced by severe trauma, but is greater in severity and duration[9] and directly proportional to the total body surface area (TBSA) burned.[10] This hyperglycemic response to burns has been shown to be associated with worsened clinical outcomes.[11] Whereas insulin therapy may help control the hyperglycemia associated with burn injury, insulin also promotes muscle anabolism and attenuates the systemic inflammatory response.[12,13] Therefore, there may be reason to believe that the burned ICU patient could benefit more from IIT than the SICU patient; however, to our knowledge, the outcome benefits associated with IIT in the adult BICU population have not been examined.

Increased age has also been shown to be associated with decreased survival in critically ill and injured patients, but the contributions of diabetes or glucose intolerance to this association have not been well studied.[14] Similarly, the efficacy of IIT in elderly SICU or BICU patients is unknown.

Our goal was to determine, through the use of a prospective cohort study, whether critically ill burn patients benefit from tight glycemic control achieved by IIT in a manner analogous to the benefits already documented in SICU patients, such as decreasing overall rates of sepsis and mortality. We also sought to determine whether the benefit of tight glycemic control with IIT is associated with a similar degree of risk of hypoglycemia in both BICU and SICU patients. Finally, we sought to examine whether the benefits of IIT are as pronounced in elderly patients as they are in younger patients.

METHODS

Study population. This study was approved by the Johns Hopkins Medicine Institutional Review Board. All patients admitted to the Johns Hopkins Bayview Medical Center SICU or BICU were evaluated for study inclusion. The IIT protocol had 3 entry criteria: (1) an adult patient with morbidity significant enough to warrant designation as a critically ill patient; (2) blood glucose level greater than 119 mg/dL; and (3) an anticipated duration of ICU stay greater than 24 hours. The IIT protocol was approved by the Pharmacy and Therapeutics Committee before its 2006 implementation in the mixed-service SICU and BICU. The protocol was implemented after a period of training for staff in both units, and was accompanied by ongoing supervision and assessment by an oversight committee with representatives of the nursing and physician staff of both units.

To evaluate the effect of tight glycemic control, we divided subjects into those whose mean blood glucose measurement on day 3 of the IIT was <150 mg/dL (tight control) and ≥150 mg/dL (poor control). To evaluate the effect of IIT on age, subjects were divided into 2 groups: younger (age <65 years) and older (age ≥65 years).

Study design. The Johns Hopkins Bayview Medical Center IIT protocol requires that the patient's blood glucose be measured at least hourly until 3 consecutive glucose values are within target glucose range of 90–120 mg/dL without requiring a change in the insulin infusion. The frequency of blood glucose determinations is dependent upon the patient's blood glucose stability, current clinical condition, and nutritional intake.

The insulin used in the protocol was regular insulin (Humulin R; Eli Lilly and Company, Indianapolis, IN), a recombinant DNA human insulin. Adjustments to the insulin infusion were made depending upon blood glucose values obtained from point of service (finger sticks), from scheduled venous sample laboratory values, and/or from arterial blood samples obtained from an indwelling catheter. The precise amount of IV insulin was determined by the algorithm in the Yale insulin infusion protocol,[3] as calculated by the ICU staff, and was recorded in the patient medical record. To assess the effect of successful glycemic control, an average blood glucose value ≤150 mg/dL on day 3 was used to define tight glycemic control and an average blood glucose value >150 mg/dL was used to define poor glycemic control as described previously.[15] The data from all patients who remained on the IIT for at least 72 hours were selected for analysis.

Data collection. Clinical and demographic information, such as diagnosis and outcome, for both SICU and BICU patients were entered into a prospectively collected secure database. Blood glucose values were recorded (point of service, lab blood glucose, and arterial blood from an indwelling catheter), and total daily IV insulin units (U) administered (U/h*h, insulin rate*hour) was recorded.

For both SICU and BICU patients, variables that have a known impact on blood glucose levels were recorded. These variables included specific medications (eg, cortisol, glucagon, 50% dextrose, and vasopressors), volume and quality of nutritional feeding, operative or interventional procedures, and incidence of sepsis or infection. For patients in the BICU, the etiology of burn injury and the percentage of TBSA were also noted. The primary outcomes recorded were incidences of sepsis, hospital deaths (in the ICU or when transferred to the surgical floor), and hypoglycemic events (<60 mg/dL). Duration of hospital stay was also noted for each patient.

Statistical analysis. The trapezoidal rule was used to calculate the integrated glucose levels over the course of each 24 hours of insulin infusion. The integrated responses were divided by 24 hours, which resulted in a mean daily glucose concentration. The total daily insulin dose was also divided by the total daily time interval of insulin infusion to obtain a mean daily rate. Standard methods were used to compute means and SEM. Differences between groups were evaluated using the Student *t* test, the Chi-square test, and the Fisher exact test. All statistical tests were 2-tailed. Data are presented as mean ± SE, and P values < .05 were regarded as statistically significant.

RESULTS

Study population. The study population consisted of adult patients admitted to the SICU or BICU and who were treated with the Johns Hopkins Bayview Medical Center IIT protocol from October 2006 to July 2007. During this 9-month interval, 667 patients were admitted to the 10-bed, mixed-service SICU, and 303 patients were admitted to the 10-bed BICU. Of these 970 patients, 79 required IIT. Of these 79 patients, 37 remained on the protocol for at least 72 hours, and comprised our study population. Of the 79 patients, 22 (60%) were in the SICU and 15 (40%) were in the BICU. Reasons for failure to continue in the IIT protocol for at least 72 hours included cessation of the protocol due to adequate glycemic control before 72 hours, transfer from ICU to the surgical floor, or death of the patient. The demographic data of our study population are presented in the Table.

Of the 22 patients admitted to the mixed-service SICU, 5 were surgical patients who had respiratory complications that included severe asthma, respiratory failure, bronchopneumonia, and bronchitis. These 22 patients also included 9 with gastrointestinal complications, 3 with oncologic problems, 3 with trauma (admitted for comorbidities), and 2 with infections after orthopedic operations. The average duration of hospital stay for the SICU patients was 24 days. Of these 22 patients, 14 (64%) were 65 years of age or older.

The 15 patients admitted to the BICU included 12 patients with thermal injury (average percentage of TBSA was 33%; range, 10–80%), 2 with toxic epidermal necrolysis, and 1 with hip osteomyelitis secondary to grade 4 pressure ulcers. The average duration of hospital stay for the 15 BICU patients was 32 days. Of these 15 patients, 9 (60%) were 65 years of age or older.

Blood glucose control. The average initial blood glucose level for patients in the SICU was 237 ± 16.1 mg/dL. This value decreased during the 72-hour study period to a mean glucose level of 162 ± 5.0, 131 ± 3.4, and 143 ± 4.2 mg/dL on days 1, 2, and 3, respectively. The insulin infusion requirements averaged 68 ± 13.8, 134 ± 28.2, and 209 ± 23.5 U on days 1, 2, and 3, respectively (Fig 1).

In the BICU, a similar decrease in mean blood glucose was observed. The mean admission blood glucose level was 211 ± 21.5 mg/dL and decreased

Table. Patients' characteristics and outcomes during hospital stay (mean + SEM)

	SICU		*BICU*	
	Tight controlled ≤150 mg/dL	*Poorly controlled >150 mg/dL*	*Tight controlled ≤150 mg/dL*	*Poorly controlled >150 mg/dL*
Number	10 (45%)	12 (56%)	5 (33%)	10 (67%)
Sex				
Male	2	6	2	9
Female	8	6	3	1
Age (yr)	64.20 ± 5.55	70.92 ± 2.78	50.6 ± 9.55	54.90 ± 3.94†
BMI (kg/m^2)	38.86 ± 5.75	37.17 ± 3.02	26.68 ± 1.16	34.14 ± 2.71
TBSA burn %	—	—	10.00 ± 2.48	44.75 ± 7.15*
Hypoglycemic events (<60 mg/dL)	0	4	2	1
Length of hospital stay (days)	17.1 ± 5.63	30.25 ± 5.81	18.8 ± 6.87	38.8 ± 9.34
Sepsis	1(10%)	7 (58%)	3 (60%)	7 (70%)
Hospital deaths	0	7 (58%)	1 (20%)	5 (50%)

No significant differences were noted in comparisons of the variables between tight and poorly controlled groups for each ICU. Only age was significantly different for the poorly controlled groups between the two ICUs ($P = .003$).
*$P \leq .005$ compared to "tightly" controlled in the same ICU.
†$P \leq .003$ compared to "poorly" controlled between the 2 ICUs. The number in () represents %.

during the 72-hour study period to a mean glucose level of 161 ± 7.6, 149 ± 4.6, and 153 ± 6.1 mg/dL on days 1, 2, and 3, respectively. Insulin infusion requirements were less in this group compared to the SICU patients, averaging 51 ± 11.7, 97 ± 13.6, and 110 ± 20.9 U on days 1, 2, and 3, respectively ($P = .005$ vs SICU for day 3; Fig 1).

To assess the effect of tight glycemic control on clinical outcome, SICU and BICU data were dichotomized by level of glycemic control. Patients in both units with a mean blood glucose level ≤150 mg/dL on day 3 were considered to have achieved tight control, whereas patients whose average blood glucose level was >150 mg/dL were considered poorly controlled. The value of 150 mg/dL was chosen because it has been used in previous studies[15,16] and approximated the mean day 3 glucose values in the study population.

Of the 22 patients admitted to the SICU, 10 (45%) achieved tight control (glucose level <150 mg/dL) by day 3 on the insulin infusion protocol (Table). Age and body mass index (BMI), which are 2 variables shown to influence insulin sensitivity and glucose kinetics, were similar in both the tightly controlled and poorly controlled groups. The mean total daily insulin for the tightly controlled group was 51 ± 11.6, 94 ± 21.5, and 172 ± 16.4 U on days 1, 2, and 3, respectively. Interestingly, we noticed that the poorly controlled group received more insulin over their 3-day course: 89 ± 26.2, 182 ± 54.2, and 220 ± 33.3 U. The poorly controlled group also had 4 hypoglycemic (<60 mg/dL) events, suggesting more difficulty with the degree of control. None of the hypoglycemic events noted in this study were accompanied by any medical sequelae.

In the BICU, only 33% of patients achieved tight control by day 3 (Table). The tightly controlled group had a greater number of female patients than the poorly controlled group, similar to the trend seen in the SICU; age and BMI were also similar. The mean daily insulin requirement for the tightly controlled group was 67 ± 13.7, 109 ± 16.9, and 110 ± 23.5 U on days 1, 2, and 3, respectively. The poorly controlled group had a lesser mean insulin infusion: 17 ± 9.4, 73 ± 17.9, 111 ± 43.1 U on days 1, 2, and 3, respectively, suggesting insufficient insulin delivery in this group.

A possible reason for a low daily insulin demand in the BICU patients is that our IIT protocol requires insulin infusion to be stopped when feedings are held. Insulin infusion was also temporarily stopped whenever a patient returned to the operating room (OR) for grafting, wound care procedures, etc. As a result, the burn patient who required frequent trips to the OR for their burn care or more extensive operative procedures was at risk for prolonged periods of cessation of the insulin infusion, with resulting hyperglycemia. The average duration of time the insulin infusion protocol was held over the 72-hour study interval in BICU patient was 3.6 hours. The poorly controlled patient group had insulin held for 4.4 ± 0.51 hours, which was significantly greater than the 2.6 ± 0.24 hours for those patients who achieved tight glycemic control ($P = .022$). Other reasons for the decreased

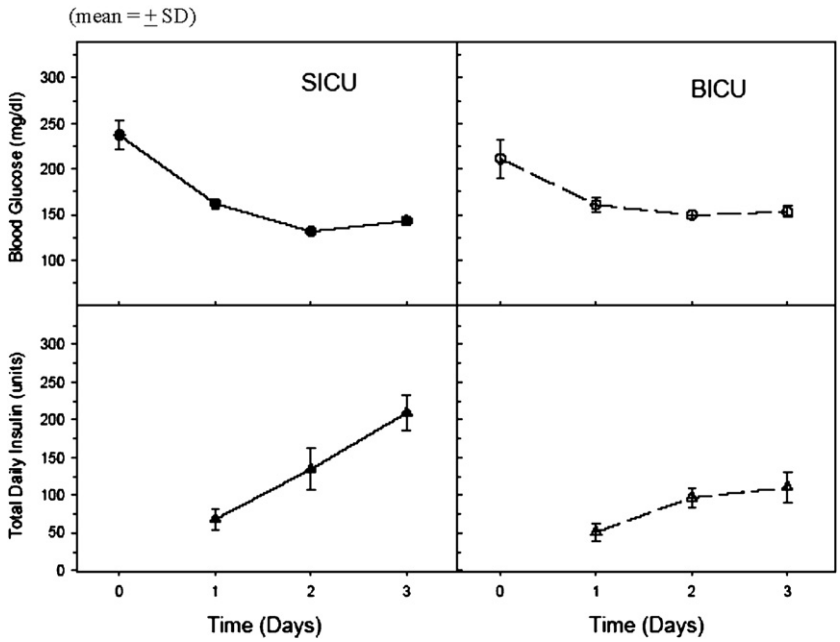

Fig 1. Average glucose levels in the upper panel and the average daily insulin requirements in the lower panel for all patients admitted to the surgical intensive care unit (SICU) (*left panels*) and the burn ICU (BICU) (*right panels*).

insulin demand may have included the relatively younger age and lower BMI seen in BICU patients compared to SICU patients (Table).

Sepsis and mortality. There was no mortality in either unit during the 72 hours of IIT. Overall, of the 37 patients, 18 (49%) had at least 1 septic episode. In the SICU, 8 patients were diagnosed with sepsis, which represented 10% of the tightly controlled group and 58% of the poorly controlled group ($P < .05$). Within the poorly controlled SICU group, all 7 SICU patients with poor glycemic control who had septic episodes ultimately died. None of the patients were septic within the study period of 72 hours after initial insulin infusion, but became septic subsequently in their hospital course.

In the BICU, septic episodes occurred in 3 of 5 patients with tight glycemic control; 2 of the septic episodes occurred during the initial 72 hours of the IIT protocol. One patient had osteomyelitis and was diagnosed with sepsis within the first 24 hours of insulin therapy. The other patient, who had a 13% TBSA severe upper body burn, became septic after 48 hours and ultimately died while in the BICU.

A total of 7 patients (70%) in the poorly controlled burn injury group developed sepsis. Of these 7 patients, 5 ultimately died due to septic complications; none of these 5 patients had a septic episode within the first 72 hours of initiating the IIT protocol.

TBSA burn. Patients who achieved tight glycemic control by day 3 had a mean value of TBSA burn of 10% ± 2.5% (including 1 patient who was in the BICU with extensive decubitus ulcers and osteomyelitis, and 2 patients with toxic epidermal necrolysis). Of the 8 thermally injured patients, 2 had burns >60% TBSA (65% and 75%). These 2 patients averaged a greater time in the OR compared to the other BICU patients and, as such, had more time with their insulin infusion suspended as per the IIT protocol. Both patients ultimately died of septic complications.

Age and mortality. The relationship of tightly and poorly controlled glucose levels with regard to sepsis and mortality as a function of age is presented in Fig 2. Of the 37 patients in our study population, 15 (41%) were tightly controlled and 22 (59%) were poorly controlled. A total of 19 (51%) were 65 years of age or older, of whom 13 (68%) were poorly controlled. Of the 13 poorly controlled elderly patients, 8 (62%) died, whereas no death occurred in the 6 elderly patients with tightly controlled glucose levels ($P = .014$).

Of the 18 patients in the younger group (<65 years of age), 9 patients were poorly controlled; 4 of these 9 patients (44%) died, 3 of whom were BICU patients with sepsis. The 1 death in the subset of poorly controlled SICU patients less than 65 years old also was due to sepsis. In the group of 9 younger SICU patients with tightly controlled

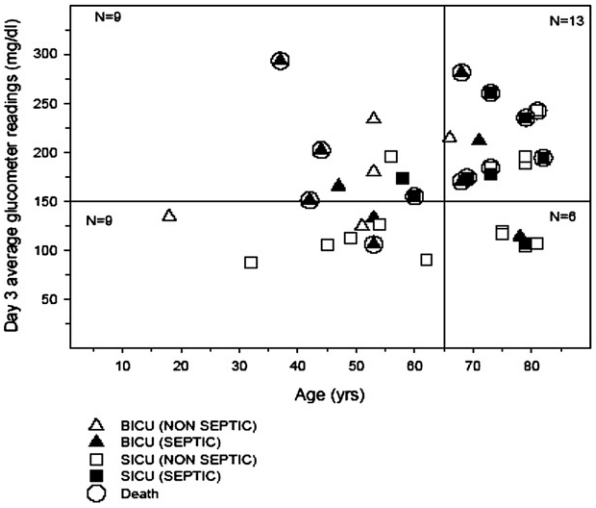

Fig 2. Scatterplot of third-day average glucose level as a function of age and glycemic control with regard to follow-up outcome of sepsis and mortality.

glucose levels, only 1 patient died and that patient had sepsis (P = 0.35 vs the younger poorly controlled group).

DISCUSSION

During the stress of critical illness, endogenous catecholamines, glucocorticoids, glucagon, and cytokine levels are all increased.[9,17] Despite normal insulin levels, the increase in stress hormones creates a state of insulin resistance by decreasing insulin receptor binding and activation, as well as the availability of glucose transporters.[18] Elevated glucagon and catecholamine levels stimulate hepatic glucose production. In addition, patients receive medications (eg, catecholamines) and nutritional support, which also increase blood glucose levels. All of these factors contribute to the development of a hyperglycemic state. Restoration of euglycemia has been shown repeatedly to reduce the incidence of hospital-acquired infection and sepsis and to increase survival in critically ill and injured patients.[1,2,15,16]

The patients in our study with a mean blood glucose ≤150 mg/dL by day 3 were considered tightly controlled, and these patients had lower hospital death rates in both the BICU (20% vs 50% in the poorly controlled group) and the SICU (0% vs 58% in the poorly controlled group). With regard to sepsis, there was a striking difference in the number of septic events in the SICU between the 2 glycemic groups (10% in the tightly controlled group and 58% in the poorly controlled group). The difference in the number of septic episodes between tightly controlled patients (60%) compared to poorly controlled patients (70%) in the BICU was less than the difference observed between the same group of patients in the SICU setting.

The failure to confirm a direct association between sepsis and death in the BICU as opposed to the SICU may be due to the relatively small number of patients in our study, as well as the greater incidence of septic episodes in all the BICU patients. Nonetheless, survival in the BICU was clearly associated with tight glycemic control, as well as with lower TBSA burn percentage and younger age.

There were a total of 7 hypoglycemic events for all patients included in this study. Interestingly, 6 of these events occurred in the poorly controlled (glucose level >150 mg/dL) groups. This finding is somewhat counterintuitive, because this group has, by definition, a greater mean blood glucose value. Episodes of hypoglycemia were routinely treated with cessation of the insulin infusion and administration of 50% IV glucose infusion. This practice invariably resulted in a rebound hyperglycemia that, in turn, required greater amounts of IV insulin infusion to control. Therefore, our protocol for hypoglycemia treatment required modification to prevent overcorrection with both IV glucose and insulin. Such revisions to the IIT protocol were made prospectively; as a result, the incidence of hypoglycemic events was greater within the first 5 months (N = 5) of the study period compared to the final 4 months (N = 2).

In an observational retrospective study of 108 trauma patients who had an ICU stay >48 hours, Gale et al[19] found a trend toward a greater mortality rate in patients with a mean 48-hour blood glucose level >140 mg/dL compared to patients with a mean glucose level <140 mg/dL (22% vs 9%). In a medical ICU, Lacherade et al[20] found that, in 105 patients who had a medical ICU stay >24 hours, poor control (defined by an average blood glucose level >130 mg/dL) was associated with a 50% mortality compared to 22% for those patients who had values ≤130 mg/dL. Furthermore, they found that the odds ratio of ICU death in patients whose blood glucose was not controlled compared with patients whose blood glucose was controlled was >3 independent of other variables. Lacherade et al[20] concluded that the greater mortality rate may be directly related to failure to maintain glucose control over time and that tighter glucose control may decrease mortality. These studies corroborated the report of Scalea et al,[16] in which a similar result was seen in a large trauma population.

These observational studies also leave open the possibility that hyperglycemia is a result of comorbidities and infectious processes rather than a direct contributor to mortality. In other words, did hyperglycemia occur as a consequence of infection/morbidity, or was hyperglycemia a risk factor for acquiring infection? A post hoc analysis of Van den Berghe et al's 2001 study[1] revealed a linear correlation between the degree of hyperglycemia and the risk of death; in a 2003 study,[21] Van den Berghe et al demonstrated that this correlation persisted after correction for insulin dose and severity of illness. Multivariate logistic regression analysis of these data confirmed the independent role of blood glucose control in achieving most of the clinical benefits of IIT and highlights the importance of lowering blood glucose levels.

Although our study did not have sufficient enrollment to support a meaningful multivariate analysis, a similar argument regarding hyperglycemia as a consequence or as a risk factor of sepsis may be made by analysis of the temporal sequence of events. For both the SICU and the BICU population under study, none of the patients who became septic and had poor glycemic control were septic within the IIT study period of 72 hours. Rather, all septic episodes occurred subsequently in the patients' hospital course. Although not definitive, it would be hard to argue that poor glycemic control was a result of sepsis that occurred 72 hours after the event.

In the landmark, randomized, prospective trial of Van den Berghe et al,[1] intention to treat with IIT was clearly associated with reduced septic complications and reduced mortality. This trial and other prospective trials demonstrate that maintenance of tight glycemic control by IIT has a significant benefit. This finding raises the possibility that insulin administration has a beneficial effect that might be due to metabolic or antiinfectious processes independent of glycemic control. Our study design attempts to control for these factors by examining only the patients treated with IIT to determine if the glycemic level achieved–*despite IV insulin administration*–correlates with improved survival. Our findings demonstrate that tight glycemic control in the ICU is predictive of survival. To our knowledge, our results also demonstrate for the first time that this benefit extends to the BICU as well as the SICU population.

However, it should be noted that studies using IIT protocols that nearly achieve tight glucose level at a concentration ≤110 mg/dL have also reported increased mortality compared to a conventional controlled group in which blood glucose levels were targeted at concentrations ≤180 mg/dL.[22] This finding may be due to an approximate 13-fold increase in the incidence of hypoglycemic events in the former group.[6]

After a major burn injury, there is a hypermetabolic response that increases glucose consumption, glycogenolysis, and proteolysis.[23] Burn injury demands an extremely high metabolic response, with energy requirements met by protein and amino acid recruitment.[24] Severely burned patients have elevated glucose production and glucose utilization almost entirely through anaerobic mechanisms.[24,25] At the cellular level, the hyperglycemic state creates additional oxidative stress and acts with other mediators to activate inflammation. Because insulin has been found to have antiinflammatory properties, the effects of hyperglycemia can be exacerbated by the relative insulin resistance caused by the metabolic component of the stress response. Reducing stress hyperglycemia has therefore become an important clinical and research topic, with the goal of improving outcomes in critically ill patients.

TBSA burn is a variable that is unique to the adult burn patient and is known to be associated with decreased patient survival. Our BICU population in whom we achieved tight control had a lower mean percentage of TBSA compared to the poorly controlled group (10% vs 45%). The association between poor glycemic control, sepsis, and severely burned patients may be related to a hyperglycemia–induced impairment in antimicrobial defense.[11] Hyperglycemia has been shown to retard wound healing in patients with diabetes mellitus[26]; therefore, diabetic burn victims could be expected to have a greater healing time, especially if the burn wound has a greater percentage of TBSA. Indeed, the poorly controlled burn victims had a longer hospital duration of stay.

There are some studies that report counterintuitive findings. In a study by Wahl et al,[27] hyperglycemia was associated with increased mortality in the SICU, although no association was observed between hyperglycemia and infection. In another study, BICU patients did not benefit from IIT with respect to mortality or ICU duration of stay, but hyperglycemia was associated with increased risk of infection.[28]

Two patients in our BICU group had a diagnosis of toxic epidermal necrolysis syndrome (TENS), a condition causing generalized epidermal necrosis, erosions of the mucous membranes, and extensive detachment of the epidermis, accompanied by severe constitutional symptoms.[29] Patients with

TENS are frequently treated in burn units and receive care that is identical to that provided to burn victims including: protection of eroded surfaces, infection control, nutritional support, and control of fluids and electrolytes.[30] TENS patients are managed in a manner that is similar to thermally injured patients, with surface area necrolysis being regarded as equal to large TBSA with deep burns. Care of these patients is focused on support and early excision and grafting of the involved skin. Of the 2 patients diagnosed with TENS in our study, both had glycemic levels that were poorly controlled, and 1 died from multiple organ failure due to the progression of sepsis.

The effect of age on the outcome of critically ill SICU and burn patients has been poorly studied. Of the 13 deaths in our study, 8 (62%) were in patients who were ≥65 years of age. A total of 64% of the SICU study population and 33% of the BICU population were ≥65 years of age. Whereas the mortality rate for patients <65 years of age was 28%, the rate for those patients >65 years of age was 42% (43% in the SICU group, 44% in the BICU group). Although our study was not sufficiently powered to address the issue of age as a separate variable, we observed that the morbidity and mortality associated with poor glycemic control was dramatically greater in both SICU and BICU elderly patients. In patients 65 years of age or older whose glycemic level was poorly controlled, the rate of mortality was 62% (Fig 2), whereas elderly patients who achieved tight glycemic control had 0 mortality.

Rellos et al[31] demonstrated that the high incidence of ICU-acquired infections (≥70%) appears to contribute to the greater mortality rate in elderly ICU patients. In addition, several reports have confirmed greater ICU mortality in the elderly.[32-36] Unfortunately, all of these studies evaluated mortality as a function of comorbidities (eg, cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease, dementia, stroke, chronic renal and hepatic insufficiency, and/or peripheral vascular diseases) but not glycemic control. In a study of 2064 ICU admissions, the incidence of infection in the SICU was 42%; when the patients were stratified by age group (<50 years, and each decade thereafter), elderly patients were not more susceptible to infections than the younger aged groups.[37] However, age was a strong predictor of mortality in patients with sepsis, and the death rate increased with each increasing decade (odds ratio, 1.38–21.9). Our data are consistent with these observations, and it can be inferred that tightly controlled glycemia in the elderly ICU patient will be especially effective in reducing the incidence of sepsis and death in this subset of patients.

There are some limitations to our study. First, only a small population of patients was analyzed in this study. Second, although the association of tight glycemic control by day 3 has been used by other researchers to predict outcomes,[1,15] the optimal interval for achievement of glycemic control and the duration of maintenance to achieve maximal survival benefit are both unknown. Finally, although the 150 mg/dL glucose criterion was convenient for this study and has been used in previous studies, there is no universally accepted value to define optimal glycemic control. Levels of recommended glycemic control range from 110 mg/dL to 180 mg/dL with various populations and studies.[1,7,8,15,38] It remains to be determined which goal is associated with the maximal benefit of reduced sepsis and death, balanced against the risk of hypoglycemia. Nonetheless, our results strongly support the concept that both SICU and BICU patients benefit from aggressive management of glycemic levels.

In conclusion, from our retrospective cohort study, we conclude that tight glycemic control is associated with reduced mortality in both the SICU (0% vs 58%) and the BICU (20% vs 50%) in patients on IIT. Patient survival in the BICU is associated with tight glycemic control, as well as a lower percentage of TBSA burn and lesser age. This preliminary study reveals an association between improved management of blood glucose and beneficial outcomes in adult burn victims, and indicates the need for a larger study to confirm these findings. In addition, our data suggest that hyperglycemia may be especially difficult to control in both elderly and burn patients, and these patients therefore may be at higher risk of sepsis and mortality. Further exploration of the benefit of tight glycemic control in the elderly in both the BICU and SICU is warranted and essential.

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