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### Increased hypoglycemia associated with renal failure during continuous intravenous insulin infusion and specialized nutritional support

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## Increased hypoglycemia associated with renal failure during continuous intravenous insulin infusion and specialized nutritional support

### Abstract

**Objective:** To evaluate glycemic control for critically ill, hyperglycemic trauma patients with renal failure who received concurrent intensive insulin therapy and continuous enteral (EN) or parenteral nutrition (PN).

**Methods:** Adult trauma patients with renal failure, who were given EN or PN concurrently with continuous graduated intravenous regular human insulin (RHI) infusion for at least 3 days were evaluated. Our conventional RHI algorithm was modified for those with renal failure by allowing greater changes in blood glucose concentrations (BG) before the infusion rate was escalated. BG was determined every 1-2 hours while receiving the insulin infusion. BG control was evaluated on the day prior to RHI infusion and for a maximum of 7 days while receiving RHI. Target BG during the RHI infusion was 70 to 149 mg/dL (3.9 to 8.3 mmol/L). Glycemic control and incidence of hypoglycemia for those with renal failure were compared to a historical cohort of critically ill, hyperglycemic trauma patients without renal failure given our conventional RHI algorithm.

**Results:** Twenty-one patients with renal failure who received the modified RHI algorithm were evaluated and compared to forty patients without renal failure given our conventional RHI algorithm. Average BG was significantly greater for those with renal failure (133 + 14 mg/dL or 7.3 + 0.7 mmol/L) compared to those without renal failure (122 + 15 mg/dL or 6.8 + 0.8 mmol/L), respectively ( $p < 0.01$ ). Patients with renal failure experienced worsened glycemic variability with 16.1 + 3.3 hours/day within the target BG range, 6.9 + 3.2 hours/day above the target BG range, and 1.4 + 1.1 hours below the target BG range compared to 19.6 + 4.7 hours/day ( $p < 0.001$ ), 3.4 + 3.0 hours/day ( $p < 0.001$ ), and 0.7 + 0.8 hours/day ( $p < 0.01$ ) for those without renal failure, respectively. Moderate hypoglycemia ( $< 60$  mg/dL or  $< 3.3$  mmol/L) occurred in 76% of patients with renal failure compared to 35% without renal failure ( $p < 0.005$ ). Severe hypoglycemia (BG  $< 40$  mg/dL or  $< 2.2$  mmol/L) occurred in 29% of patients with renal failure compared to none of those without renal failure ( $p < 0.001$ ).

**Conclusion:** Despite receiving a modified RHI infusion, critically ill trauma patients with renal failure are at higher risk for developing hypoglycemia and experience more glycemic variability than patients without renal failure.

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Increased Hypoglycemia Associated with Renal Failure during Continuous Intravenous  
Insulin Infusion and Specialized Nutrition Support

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0.001), and  $0.7 \pm 0.8$  hours/day ( $p < 0.01$ ) for those without renal failure, respectively. Moderate hypoglycemia ( $< 60$  mg/dL or  $< 3.3$  mmol/L) occurred in 76% of patients with renal failure compared to 35% without renal failure ( $p < 0.005$ ). Severe hypoglycemia (BG  $< 40$  mg/dL or  $< 2.2$  mmol/L) occurred in 29% of patients with renal failure compared to none of those without renal failure ( $p < 0.001$ ).

**Conclusion:** Despite receiving a modified RHI infusion, critically ill trauma patients with renal failure are at higher risk for developing hypoglycemia and experience more glycemic variability than patients without renal failure.

## **Introduction**

Critically ill trauma patients often develop insulin resistance and experience hyperglycemia.[1] Despite controversy regarding the optimal target blood glucose concentration range for various critically ill patient populations[2,3], evidence of improved morbidity and mortality has been established for critically ill trauma patients who receive modest glycemic control (e.g., < 150 mg/dL or 8.3 mmol/L).[2,4-6] Hyperglycemia during critical illness may be further complicated by renal failure (acute kidney injury or the presence of chronic kidney disease). Patients with renal failure have been shown to develop hyperglycemia and insulin resistance.[7-9] Conversely, patients with renal failure have been reported to be susceptible to the development of hypoglycemia[10-13] with decreased insulin requirements compared to those with normal renal function.[14,15] As a result of these divergent mechanisms, the intent of this retrospective study was to evaluate the extent of glycemic control and incidence of hypoglycemia for critically ill, hyperglycemic trauma patients with renal failure who received concurrent intensive insulin therapy and specialized nutrition support.

## **Materials and Methods**

Adult patients,  $\geq 18$  years of age, admitted to the Presley Memorial Trauma Center at the Regional Medical Center at Memphis between February, 2008 until May 2009, who were referred to the Nutrition Support Service for specialized nutrition support, and who required intensive insulin therapy were identified for potential inclusion into the study. Patients studied included those with acute kidney injury (AKI) according to the RIFLE criteria[16] or with Stage V chronic kidney disease (CKD) as evidenced by a

history of outpatient hemodialysis, treated for hyperglycemia with a graduated continuous intravenous insulin infusion algorithm, and concurrently given continuous enteral nutrition (EN) or parenteral nutrition (PN). Patients were excluded if they received supplemental intermediate-acting or long-acting insulin therapy (e.g., neutral protamine hagedorn or insulin glargine) during the study observation period, received intermittent or bolus EN, had an ad-libitum oral diet intake  $> 500$  kcal/d (2,093 kJ/d), or received  $< 72$  hours of continuous intravenous insulin therapy. Adult patients without renal failure admitted to the trauma intensive care unit who received our conventional graduated intravenous infusion algorithm (Table 1) from February, 2006 to April, 2007 served as a historical cohort control group.[17] Determination for the need for hemodialysis was done by the nephrology consultative service. Conventional hemodialysis was completed within a four hour time period with the patients re-evaluated daily for additional hemodialysis or hemofiltration. Continuous renal replacement therapy or peritoneal dialysis was not available at our institution.

Patients who were initially selected to receive continuous intravenous insulin infusion therapy included those who had a serum or blood glucose concentration (BG)  $\geq 180$  mg/dL (10 mmol/L) before the initiation of specialized nutrition support, hyperglycemia  $\geq 150$  mg/dL (8.3 mmol/L) with a past medical history of diabetes mellitus, or persistent hyperglycemia  $\geq 150$  mg/dL (8.3 mmol/L) during EN or PN despite attempts to minimize the hyperglycemia. Efforts to reduce hyperglycemia included the use of a diabetic EN formulation whenever a specialized EN formula (e.g., immune-enhancing diet or renal failure formula) was not indicated or a low dextrose-containing PN solution with added regular human insulin, elimination of dextrose from

large volume parenteral solutions and small volume parenteral medications whenever possible, and implementation of either an insulin infusion or sliding scale regular human insulin as previously described.[17] Point-of-care BG concentrations were determined hourly by the glucose dehydrogenase method using the Accu-Chek® Inform System (Roche Diagnostics Corporation, Indianapolis, IN, USA) during the infusion.

The continuous intravenous insulin infusion was prepared by mixing 100 mL of 0.9% sodium chloride injection with 100 units of regular human insulin to achieve a final concentration of 1 unit per mL. The insulin infusion was initiated at a rate of 2 to 4 units/h and titrated thereafter in an effort to maintain the BG within the target range of 70 to 149 mg/dL (3.9 to 8.3 mmol/L). Time to achieve BG control was determined from the difference between the hours of initiation of the insulin infusion to the hour whereby two consecutive hourly BG measurements were less than 150 mg/dL (8.3 mmol/L). After stability in BG concentrations within the target BG range with a consistent RHI infusion rate and the goal nutrition support regimen was reached, BG measurement monitoring was extended from hourly to every two hours. Moderate hypoglycemia and severe hypoglycemia were defined as a BG concentration of < 60 mg/dL (3.3 mmol/L) and < 40 mg/dL (2.2 mmol/L), respectively.

The safety and efficacy of our graduated intravenous insulin infusion protocol for our critically ill trauma patients without renal failure receiving specialized nutrition support has been previously established[17] and served as the historical comparative control group for this study. We empirically observed frequent development of severe hypoglycemia when our original insulin infusion algorithm was employed for trauma patients with renal failure. Resultantly, the algorithm was modified for trauma patients

with renal failure by allowing a greater changes in BG (e.g., 50 mg/dL or 2.8 mmol/L instead of 25 mg/dL or 1.4 mmol/L increments) before the insulin infusion rate was escalated. Details regarding the modified and conventional graduated intravenous insulin infusion algorithms are given in Table 1.

Patients were preferentially given EN by a small-bore, nasogastric/nasoenteric feeding tube or jejunostomy. PN was given when the patient was unable to tolerate EN or when EN was contraindicated. If the EN or PN regimen was temporarily or abruptly discontinued, a 5% dextrose-containing large-volume parenteral solution was administered at the same infusion rate as the feeding formulation in an effort to prevent hypoglycemia. If the patient's PN or EN was to be discontinued for any significant portion of time, the continuous intravenous insulin infusion was discontinued. Serum laboratories were obtained from each patient on a daily basis. The blood was obtained at approximately 0300 via an indwelling arterial or venous catheter while the patient lay supine in bed. Laboratory tests were ordered by the patient's primary service or the Nutrition Support Service and performed by the hospital laboratory as part of the patient's routine clinical care. The Injury Severity Score[18] was obtained from the Trauma Registry at the Regional Medical Center at Memphis. The presence of sepsis was documented according to the 2001 International Sepsis Definitions Conference.[19]

At the time of enrollment into the study, the patient's hospital chart, electronic medical records, and bedside clinical data were reviewed. Data were recorded for the day prior to starting the intravenous insulin infusion and for a maximum of eight days while receiving the infusion. Mean BG measurements were averaged for each day. Data recorded for Day 0 was considered a partial day beginning when the intravenous insulin

infusion was initiated. The number of units of regular human insulin given daily was also recorded. If the patient received PN, the amount of insulin received from the PN formulation was added to amount received from the infusion to determine total units of regular human insulin received.

The study was approved and conducted in accordance with the guidelines established by the Institutional Review Board of the University of Tennessee Health Science Center. Because all measurements from this observational study were performed as part of the routine clinical care of the patient and because confidentiality procedures for the patient were maintained, the requirement for informed consent was waived. Data were analyzed using SigmaPlot<sup>®</sup> for Windows version 11.2 (Systat Software, Inc., Point Richmond, CA). Data were evaluated for normality of distribution by using the Shapiro-Wilk test. Independent variables were compared by applying the t-test for unpaired variables if the data were normally distributed or Mann-Whitney U test if they were not normally distributed. Two-way repeated measures analysis of variance with post-hoc pair-wise comparisons using the Student-Newman-Keuls test were used for comparing serial data within and between groups. Differences between groups for nominal data were analyzed by either Chi-Square analysis or Fisher Exact test. Continuous data are expressed as mean  $\pm$  S.D. A p value of 0.05 or less indicated statistical significance.

## **Results**

Twenty-one consecutive hyperglycemic adult patients admitted to the trauma intensive care unit from February 2008 to May 2009, referred to the nutrition support service, who developed AKI (n=18) or had pre-existing Stage V CKD (n=3) and who

required the modified intravenous insulin infusion algorithm were evaluated. Sepsis or ischemia from hemorrhagic or hypovolemic shock were responsible for the pathogenesis of acute kidney injury in these patients. Eight patients required intermittent hemodialysis during the continuous intravenous insulin therapy. Data from a previously published study[17] with forty consecutive hyperglycemic adult patients without renal failure admitted to the trauma intensive care unit who received our conventional intravenous infusion algorithm served as a historical control group (Table 2). All patients in both groups were ventilator-dependent and none had evidence of significant liver disease. Patients were given fentanyl and midazolam for analgesia and sedation. Eight patients with renal failure and twenty-two patients in the historical control group initially received propofol for the management of increased intracranial pressure from traumatic brain injury. A significant proportion of each population had a past medical history of diabetes mellitus (52% versus 40% for the renal failure and normal renal function groups, respectively) and was older than our typical trauma patient population[20,21] with a mean age of 60 and 57 years, respectively (Table 2). No differences in age, weight, injury severity score, presence of diabetes mellitus, incidence of sepsis, or other clinical markers that may explain differences in glycemic control were found between groups (Table 2). The renal failure group had a higher proportion of African-Americans (57%) compared to 25% of patients in the control group ( $p = 0.04$ ). Not surprisingly, mean serum creatinine concentration was significantly greater for the renal failure group (e.g., 3.2 mg/dL versus 1.2 mg/dL or 283  $\mu\text{mol/L}$  versus 106  $\mu\text{mol/L}$ , respectively,  $p < 0.001$ ) and the predicted creatinine clearance by Cockcroft-Gault equation[22] was also substantially lower (36 mL/min versus 73 mL/min, respectively,  $p < 0.001$ ; Table 2).

The continuous intravenous insulin infusion was started approximately 3 days after initiation of specialized nutrition support for both groups after failure to control hyperglycemia with conventional conservative management. Patients from both groups required several days of a continuous intravenous insulin infusion for an average of ~100 units daily and received similar amounts of carbohydrate (Table 3; Figure 1). Patients achieved the target BG concentrations within several hours for both groups ( $p = \text{N.S.}$ ). Mean BG concentration during the observation period for the renal failure group was greater than the control population (133 mg/dL versus 122 mg/dL or 7.3 mmol/L versus 6.8 mmol/L,  $p < 0.01$ , Table 3). Average daily BG concentrations were also greater for the AKI group compared to control (Figure 1,  $p < 0.05$ ).

Differences in BG control and variability were evident as patients with renal failure had less time within the target BG concentration range (16 hrs/d versus 20 hrs/d, respectively, Table 3;  $p < 0.001$ ). Additionally, patients with renal failure exhibited twice as much time above (7 hrs versus 3 hrs, respectively,  $p < 0.001$ ) and below (1.4 versus 0.7 hrs, respectively,  $p < 0.01$ ) the target BG concentration range (Table 3).

Hypoglycemic (BG  $< 60$  mg/dL or 3.3 mmol/L) episodes were evident in 56 of 2,536 (2.21%) BG measurements for patients with renal failure compared to 23 of 4,140 (0.56%) for those without renal failure ( $p < 0.001$ ). Seven of the 56 episodes of hypoglycemia for patients with renal failure were attributed to protocol violations. Severe hypoglycemia (BG  $< 40$  mg/dL or 2.2 mmol/L) occurred in 9 of 2,536 (0.35%) for those with renal failure in contrast to 0 of 4,140 BG measurements for those without renal failure ( $p < 0.001$ ). Two hypoglycemic patients with renal failure were reported to be symptomatic with improvement following administration of 50 g of intravenous dextrose.

Twenty-nine percent of patients with renal failure developed at least one episode of severe hypoglycemia whereas none of those without renal failure developed severe hypoglycemia ( $p < 0.001$ , Table 3). There were no significant differences in patient characteristics, average BG concentration, injury severity score, amount of insulin or carbohydrate received among those who developed severe hypoglycemia compared to those who did not experience severe hypoglycemia ( $p = \text{NS}$ , Table 4). None of the patients received medications commonly known to potentially induce hypoglycemia (e.g., trimethoprim-sulfamethoxazole, pentamidine, oral sulfonylureas, metformin, levofloxacin, quinine, or disopyramide)[23] during the study period. Five patients from each group received intravenous vasopressor and/or inotropic support. None of the patients received other medications known to induce hyperglycemia (e.g., corticosteroids, thiazide diuretics, protease inhibitors,  $\beta$ -adrenergic blockers, clozapine, or olanzapine)[24] during the study observation period.

## **Discussion**

Hyperglycemia is a common complication in critically ill trauma patients receiving specialized nutrition support.[17] If the hyperglycemia remains uncontrolled, adverse effects from hyperglycemia may occur independently of the extent of injury.[25-28] Therefore, critically ill, hyperglycemic trauma patients receiving EN or PN are also given a continuous intravenous insulin infusion in an effort to lower their BG to less than 140 to 150 mg/dL (7.8 to 8.3 mmol/L).[4-6] However, recent trends towards an increasing prevalence of hypoglycemia with intensive insulin therapy[2,29-32] has prompted clinicians to critically re-evaluate their current management of hyperglycemia.

Although the development of severe hypoglycemia has been associated with increased mortality[11,13,33-36], this association is not conclusively causal and may be attributable to impending death from multiple organ failure syndrome rather than an incidental short-term episode of hypoglycemia from intensive insulin therapy.[37-39] Even with the lack of conclusive evidence of increased mortality from hypoglycemia, severe hypoglycemia can result in neuroglycopenic consequences including seizures, coma, and death and should be avoided.

Defining hypoglycemia solely on the serum or blood glucose concentration can be misleading as the glycemic threshold for physiological responses to hypoglycemia such as glycemic counter-regulatory hormone production, initiation of autonomic and neurologic symptoms, and onset of deterioration in cognitive function is variable among normal humans.[40] A BG of ~70 mg/dL (3.9 mmol/L) or less has been shown to increase glycemic counter-regulatory hormone secretion without the presence of autonomic or neuroglycopenic symptoms until a BG of ~ 60 mg/dL (3.3 mmol/L) or less was achieved.[40] Based on these data, we defined a BG of less than 60 mg/dL (3.3 mmol/L) as clinically relevant (e.g., moderate hypoglycemia) whereby the intravenous insulin infusion was to be stopped and additional intravenous glucose immediately given to the patient irrespective of presence or absence of hypoglycemic symptoms (Table 1). The definition of severe hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L) concurs with the criteria used in the large intensive insulin therapy trials[2,3,29-31] and is clearly associated with cognitive function decline[40] and potentially seizures, coma, and death.

After observing several cases of severe hypoglycemia with the use of our conventional graduated continuous insulin infusion[17] in patients with renal failure, we

modified our original algorithm by allowing greater changes in BG before the insulin infusion dose was escalated in an effort to reduce the risk for hypoglycemia (Table 1). With use of this modified algorithm, average daily BG concentrations were significantly higher for those with renal failure (Figure 1). Despite a higher mean BG concentration, three-fourths of our hyperglycemic trauma patients with renal failure experienced at least one episode of moderate hypoglycemia and nearly one-third had an episode of severe hypoglycemia (Table 3). This high prevalence of hypoglycemia was unlike that observed in our control cohort population whereby only one third of the population experienced an episode of moderate hypoglycemia and none developed severe hypoglycemia (Table 3). Data extracted from the large intensive insulin therapy trials[2,3,29-31] may indirectly support our observations. Table 5 summarizes the reported incidence of renal failure in these trials along with the incidence of severe hypoglycemia. Both the Leuven 2[41] and VISEP[29] trials reported the highest incidence of acute kidney injury at 20% and 31% respectively of those who received intensive insulin therapy. These two investigations also had the highest incidence of severe hypoglycemia (18.7% and 17%, respectively) of the major trials. However, further investigation by these groups is necessary to be certain whether this association between renal failure and severe hypoglycemia is congruent with our findings as multiple factors may have been involved in the development of hypoglycemia.

Less hypoglycemia occurred for our patients without significant renal failure despite a more aggressive continuous intravenous insulin infusion algorithm (Table 1). However, it is additionally plausible that the observed rate of hypoglycemia may be attributable to the insulin infusion algorithm itself used for patients with renal failure.

Although the escalation in insulin infusion rate is slower for the modified algorithm, the de-escalation dosing portion of the algorithm remained the same. Following the analysis of these data as part of our quality improvement procedures for the Nutrition Support Service at the Regional Medical Center at Memphis, the continuous intravenous insulin infusion algorithm designed for patients with renal failure as described in Table 1 was terminated with the subsequent re-design and implementation of a new algorithm in an effort to avoid hypoglycemia while striving to achieve acceptable glycemic control is ongoing. Whether altering the algorithm to reflect a de-escalation in insulin infusion rate sooner for patients without renal failure will result in less hypoglycemia with maintenance of BG < 150 mg/dL (8.3 mmol/L) requires further study.

The presence of AKI or CKD complicates glycemic control. Worsening hyperglycemia from insulin resistance with an increase in associated mortality has been reported for patients with AKI.[7-9] Conversely, insulin is metabolized, in part, by the kidney and reduced renal function has resulted in a prolonged elimination half-life[14,42-44] which may result in hypoglycemia.[32] These divergent metabolic effects magnify the difficulty for achieving safe and effective glycemic control for critically ill trauma patients with AKI or CKD receiving specialized nutrition support. Patients with renal failure in our study had less favorable glycemic control than control patients with significantly less hours in the target BG range (16 hrs versus 20 hours daily) and twice as many average hours above (7 hrs versus 3 hrs) and below (1.4 hrs versus 0.7 hrs) the target range (Table 3).

The kidney has an important role in the metabolism of insulin and accounts for approximately 50% of its clearance from the systemic circulation.[45] Insulin is readily

filtered by the glomerulus and then reabsorbed or degraded by the proximal peritubular epithelial and endothelial cell membranes with less than 1% of the filtered insulin appearing in the urine.[46] About one-third of the total renal clearance of insulin occurs from receptor-mediated post-glomerular, peritubular circulation[45] resulting in greater renal clearance of insulin than the glomerular filtration rate.[46] When the glomerular filtration rate decreases to ~40 to 50 mL/min, renal insulin clearance substantially declines.[43,46]

Impaired insulin clearance from renal failure may not be the sole factor leading to or influencing recovery from hypoglycemia during continuous intravenous insulin infusion. Historical studies suggested renal glucose release accounted for only 10% of total glucose appearance and supported the concept that the kidney was a minor gluconeogenic organ.[47,48] However, more recent data indicates that the kidney represents an important organ in glucose regulation.[49-52] Isotope studies in healthy subjects demonstrated that renal glucose release accounts for 28% of systemic glucose appearance in the basal post-absorptive state.[52] During hypoglycemia, increases in plasma glucagon and circulating levels of catecholamines occur in an effort to increase blood glucose concentration via glycogenolysis and gluconeogenesis. Autonomic nervous system activation from hypoglycemia will result in gluconeogenesis and net glucose release from the kidney.[49-52]

These phenomena may explain previous observations that include a five-fold higher incidence in hypoglycemia for insulin-dependent diabetics with a serum creatinine  $\geq 1.5$  mg/dL (133  $\mu$ mol/L) compared to insulin-dependent diabetics without kidney injury[53], decreased insulin requirements of diabetic patients with impaired renal

function[14], hypoglycemic events observed in non-diabetic patients with renal insufficiency[46,54], a four-fold increase in the risk of hypoglycemia during intensive insulin therapy for patients with AKI[55], an odds ratio of 14 for hypoglycemia for patients receiving intensive insulin therapy during continuous renal replacement therapy[32], and data before the era of intensive insulin therapy indicating that half of hospitalized patients with hypoglycemia also had CKD.[11] These metabolic aberrations may also explain the 76% incidence of moderate hypoglycemia and 29% incidence of severe hypoglycemia for those with renal failure despite receiving a “modified” intravenous insulin infusion algorithm in our study.

This study has its limitations. The use of a historical control population that received a continuous intravenous insulin infusion exhibited differences from the renal failure group beyond renal function including a higher proportion of Caucasians as opposed to the current study with a higher proportion of African-Americans and a higher mortality rate than the current renal failure group. The higher than expected mortality rate of the historical control group was likely due to our extremely stringent use of continuous intravenous insulin infusion therapy at that time due to our lack of experience with the newly designed algorithm which was reserved for those who failed all conventional means of glycemic control. This inclusion criterion likely led to selection bias towards a more critically ill population than that identified by injury severity score alone. Additionally, the renal failure group contained eighteen patients with AKI and three with a history of CKD. It is unclear whether critically ill patients with AKI or CKD respond physiologically similar to each other to glycemic loads and insulin therapy during metabolic stress. Finally, the use of point-of-care blood glucose measurements is

not as accurate as serum glucose determinations from arterial blood samples and may result in about a 10% overestimation of actual glucose concentrations thereby missing potential hypoglycemic episodes.[56-58]

Our work calls attention to the fragility of glycemic control for critically ill patients with renal failure. Clinicians should be cautioned regarding the routine use of continuous intravenous insulin infusion algorithms designed in patients with adequate renal function. The physiologic mechanism(s) responsible for hypoglycemia during concurrent continuous intravenous insulin therapy and specialized nutrition support for patients with renal failure and the development of a safe and efficacious intravenous insulin infusion algorithm deserves further study.

## **Conclusions**

Glycemic control for the critically ill, hyperglycemic trauma patient with renal failure is extremely challenging. Seventy-six percent of hyperglycemic patients with renal failure treated with a continuous intravenous insulin infusion had an occurrence of moderate hypoglycemia (BG < 60 mg/dL or 3.3 mmol/L) and 29% experienced an episode of severe hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L) compared to 35% and 0%, respectively, of hyperglycemic trauma patients without renal failure. This increase in hypoglycemic episodes occurred despite the use of a modified insulin infusion algorithm designed to provide a slower escalation in insulin infusion dosage rates than our conventional algorithm. The use of continuous intravenous insulin therapy should be used with extreme caution for hyperglycemic patients with renal failure due to the excessively high risk for hypoglycemia.

**References**

- [1] Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW. Mechanisms of insulin resistance following injury. *Ann Surg* 1982;196:420-435.
- [2] Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-1297.
- [3] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359-1367.
- [4] Bochicchio GV, Joshi M, Bochicchio KM, Pyle A, Johnson SB, Meyer W, Lumpkins K, Scalea TM. Early hyperglycemic control is important in critically injured trauma patients. *J Trauma* 2007;63:1353-1358; discussion 1358-1359.
- [5] Collier B, Diaz J, Jr., Forbes R, Morris J, Jr., May A, Guy J, Ozdas A, Dupont W, Miller R, Jensen G. The impact of a normoglycemic management protocol on clinical outcomes in the trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2005;29:353-358; discussion 359.
- [6] Scalea TM, Bochicchio GV, Bochicchio KM, Johnson SB, Joshi M, Pyle A. Tight glycemic control in critically injured trauma patients. *Ann Surg* 2007;246:605-610; discussion 610-602.
- [7] Basi S, Pupim LB, Simmons EM, Sezer MT, Shyr Y, Freedman S, Chertow GM, Mehta RL, Paganini E, Himmelfarb J, Ikizler TA. Insulin resistance in critically

- ill patients with acute renal failure. *Am J Physiol Renal Physiol* 2005;289:F259-264.
- [8] DeFronzo RA, Tobin JD, Rowe JW, Andres R. Glucose intolerance in uremia. Quantification of pancreatic beta cell sensitivity to glucose and tissue sensitivity to insulin. *J Clin Invest* 1978;62:425-435.
- [9] Frohlich J, Schollmeyer P, Gerok W. Carbohydrate metabolism in renal failure. *Am J Clin Nutr* 1978;31:1541-1546.
- [10] Arem R. Hypoglycemia associated with renal failure. *Endocrinol Metab Clin North Am* 1989;18:103-121.
- [11] Fischer KF, Lees JA, Newman JH. Hypoglycemia in hospitalized patients. Causes and outcomes. *N Engl J Med* 1986;315:1245-1250.
- [12] Garber AJ, Bier DM, Cryer PE, Pagliara AS. Hypoglycemia in compensated chronic renal insufficiency. Substrate limitation of gluconeogenesis. *Diabetes* 1974;23:982-986.
- [13] Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007;35:2262-2267.
- [14] Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. *Diabet Med* 2003;20:642-645.
- [15] Naschitz JE, Barak C, Yeshurun D. Reversible diminished insulin requirement during acute renal failure. *Postgrad Med J* 1983;59:269-271.
- [16] Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007;35:1837-1843; quiz 1852.

- [17] Dickerson RN, Swiggart CE, Morgan LM, Maish GO, 3rd, Croce MA, Minard G, Brown RO. Safety and efficacy of a graduated intravenous insulin infusion protocol in critically ill trauma patients receiving specialized nutritional support. *Nutrition* 2008;24:536-545.
- [18] Baker SP, O'Neill B, Haddon W, Jr., Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974;14:187-196.
- [19] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250-1256.
- [20] Dickerson RN, Mitchell JN, Morgan LM, Maish GO, 3rd, Croce MA, Minard G, Brown RO. Disparate response to metoclopramide therapy for gastric feeding intolerance in trauma patients with and without traumatic brain injury. *JPEN J Parenter Enteral Nutr* 2009;33:646-655.
- [21] Lindsey KA, Brown RO, Maish GO, 3rd, Croce MA, Minard G, Dickerson RN. Influence of traumatic brain injury on potassium and phosphorus homeostasis in critically ill multiple trauma patients. *Nutrition* 2009.
- [22] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
- [23] Murad MH, Coto-Yglesias F, Wang AT, Sheidaee N, Mullan RJ, Elamin MB, Erwin PJ, Montori VM. Clinical review: Drug-induced hypoglycemia: a systematic review. *J Clin Endocrinol Metab* 2009;94:741-745.
- [24] Luna B, Feinglos MN. Drug-induced hyperglycemia. *Jama* 2001;286:1945-1948.

- [25] Bochicchio GV, Sung J, Joshi M, Bochicchio K, Johnson SB, Meyer W, Scalea TM. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. *J Trauma* 2005;58:921-924.
- [26] Diaz JJ, Jr., Norris PR, Collier BR, Berkes MB, Ozdas A, May AK, Miller RS, Morris JA, Jr. Morbid obesity is not a risk factor for mortality in critically ill trauma patients. *J Trauma* 2009;66:226-231.
- [27] Wahl WL, Taddonio M, Maggio PM, Arbabi S, Hemmila MR. Mean glucose values predict trauma patient mortality. *J Trauma* 2008;65:42-47; discussion 47-48.
- [28] Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. *J Trauma* 2004;56:1058-1062.
- [29] Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-139.
- [30] Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chiolero R. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009;35:1738-1748.

- [31] Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-461.
- [32] Vriesendorp TM, van Santen S, DeVries JH, de Jonge E, Rosendaal FR, Schultz MJ, Hoekstra JB. Predisposing factors for hypoglycemia in the intensive care unit. *Crit Care Med* 2006;34:96-101.
- [33] Alamgir S, Volkova NB, Peterson MW. Prognostic value of low blood glucose at the presentation of *E. coli* bacteremia. *Am J Med* 2006;119:952-957.
- [34] Kagansky N, Levy S, Rimon E, Cojocaru L, Fridman A, Ozer Z, Knobler H. Hypoglycemia as a predictor of mortality in hospitalized elderly patients. *Arch Intern Med* 2003;163:1825-1829.
- [35] Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, Masoudi FA, Marso SP, Spertus JA. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation* 2008;117:1018-1027.
- [36] Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005;26:1255-1261.
- [37] Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality. *Crit Care Med* 2009;37:2536-2544.
- [38] Mowery NT, Guillaumondegui OD, Gunter OL, Diaz JJ, Jr., Collier BR, Dossett LA, Dortch MJ, May AK. Severe hypoglycemia while on intensive insulin

- therapy is not an independent predictor of death after trauma. *J Trauma* 2010;68:342-347.
- [39] Vriesendorp TM, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, Schultz MJ, Rosendaal FR, Hoekstra JB. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006;34:2714-2718.
- [40] Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 1991;260:E67-74.
- [41] Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006;55:3151-3159.
- [42] Fuss M, Bergans A, Brauman H, Toussaint C, Vereerstraeten P, Franckson M, Corvilain J. <sup>125</sup>I-insulin metabolism in chronic renal failure treated by renal transplantation. *Kidney Int* 1974;5:372-377.
- [43] Rabkin R, Simon NM, Steiner S, Colwell JA. Effect of renal disease on renal uptake and excretion of insulin in man. *N Engl J Med* 1970;282:182-187.
- [44] Silvers A, Swenson RS, Farquhar JW, Reaven GM. Derivation of a three compartment model describing disappearance of plasma insulin-<sup>131</sup>I in man. *J Clin Invest* 1969;48:1461-1469.
- [45] Duckworth WC, Bennett RG, Hamel FG. Insulin degradation: progress and potential. *Endocr Rev* 1998;19:608-624.

- [46] Mak RH, DeFronzo RA. Glucose and insulin metabolism in uremia. *Nephron* 1992;61:377-382.
- [47] Stumvoll M, Meyer C, Mitrakou A, Nadkarni V, Gerich JE. Renal glucose production and utilization: new aspects in humans. *Diabetologia* 1997;40:749-757.
- [48] Wahren J, Felig P. Renal substrate exchange in human diabetes mellitus. *Diabetes* 1975;24:730-734.
- [49] Cersosimo E, Garlick P, Ferretti J. Renal glucose production during insulin-induced hypoglycemia in humans. *Diabetes* 1999;48:261-266.
- [50] Cersosimo E, Garlick P, Ferretti J. Abnormal glucose handling by the kidney in response to hypoglycemia in type 1 diabetes. *Diabetes* 2001;50:2087-2093.
- [51] Meyer C, Dostou JM, Gerich JE. Role of the human kidney in glucose counterregulation. *Diabetes* 1999;48:943-948.
- [52] Stumvoll M, Chintalapudi U, Perriello G, Welle S, Gutierrez O, Gerich J. Uptake and release of glucose by the human kidney. Postabsorptive rates and responses to epinephrine. *J Clin Invest* 1995;96:2528-2533.
- [53] Muhlhauser I, Toth G, Sawicki PT, Berger M. Severe hypoglycemia in type I diabetic patients with impaired kidney function. *Diabetes Care* 1991;14:344-346.
- [54] White MG, Kurtzman NA. Hypoglycemia in diabetes with renal insufficiency. *Jama* 1971;215:117.
- [55] Thomas G, Rojas MC, Epstein SK, Balk EM, Liangos O, Jaber BL. Insulin therapy and acute kidney injury in critically ill patients a systematic review. *Nephrol Dial Transplant* 2007;22:2849-2855.

- [56] Hoedemaekers CW, Klein Gunnewiek JM, Prinsen MA, Willems JL, Van der Hoeven JG. Accuracy of bedside glucose measurement from three glucometers in critically ill patients. *Crit Care Med* 2008;36:3062-3066.
- [57] Meynaar IA, van Spreuwel M, Tangkau PL, Dawson L, Sleswijk Visser S, Rijks L, Vlieland TV. Accuracy of AccuChek glucose measurement in intensive care patients. *Crit Care Med* 2009;37:2691-2696.
- [58] Wahl HG. How accurately do we measure blood glucose levels in intensive care unit (ICU) patients? *Best Pract Res Clin Anaesthesiol* 2009;23:387-400.

**Table 1** Graduated continuous intravenous insulin infusion protocols

Conventional algorithm[17]		Modified algorithm for renal failure*	
BG , mg/dL (mmol/L)	Intervention	BG (mg/dL) (mmol/L)	Intervention
< 60 <sup>§</sup> (< 3.3)	Stop RHI, give ½ amp D50W	< 60 (< 3.3)	Stop RHI, give ½ amp D50W
61 – 100 <sup>§</sup> (3.4 – 5.6)	Decrease RHI by 50%	61 – 100 (3.4 – 5.6)	Decrease RHI by 50%
101 – 125 (5.7 – 6.9)	No Change	101 – 125 (5.7 – 6.9)	No Change
126 – 175 (7.0 – 9.7)	Increase RHI by 1 unit/hr	126 - 175 (7.0 – 9.7)	Increase RHI by 1 unit/hr
176 – 200 (9.8 – 11.1)	Increase RHI by 2 units/hr	176 – 225 (9.8 – 12.5)	Increase RHI by 2 units/hr
201 – 225 (11.2 – 12.5)	Increase RHI by 3 units/hr	226 – 275 (12.6 – 15.3)	Increase RHI by 3 units/hr
226 – 250 (12.6 – 13.9)	Increase RHI by 4 units/hr	276 – 325 (15.4 – 18.0)	Increase RHI by 4 units/hr
251 – 275 (14.0 – 15.3)	Increase RHI by 5 units/hr	> 325 (> 18.0)	Increase RHI by 4 units/hr and call MD
276 – 300 (15.4 – 16.7)	Increase RHI by 6 units/hr		
> 300 (> 16.7)	Increase RHI by 6 units/hr and call MD		

<sup>§</sup>Deviates from original publication[17]: BG < 70 mg/dL and BG 70 to 100 mg/dL. \*This algorithm is not recommended for use in patients with acute kidney injury or chronic renal insufficiency. We subsequently have modified this algorithm following this study in an effort to develop a safe and effective RHI infusion algorithm for patients with acute kidney injury or chronic renal insufficiency requiring specialized nutrition support.

Additionally, we have plans to modify both our conventional and modified algorithms to provide 1 amp of D50W (50 g) for a BG  $\leq$  40 mg/dl (2.2 mmol/L) with subsequent BG checks every 30 minutes until the BG is  $>$  60 mg/dL.

**Table 2** Patient demographics: Patients without renal failure (RF) versus those with RF

Variable	Without RF (n = 40)	With RF (n = 21)	P
Male/Female (n/n)	33/7	19/2	NS
Race			
Caucasian (n)	29	9	0.04
African-American (n)	10	12	
Hispanic (n)	1	0	
Diagnosis			
MVA (n)	27	7	NS
Fall (n)	6	5	
GSW (n)	3	5	
Other (n)	4	4	
History of DM (n)	16 (40%)	11 (52%)	NS
Age (yrs)	57 ± 16	60 ± 16	NS
Weight (kg)	99 ± 33	100 ± 30	NS
BMI (kg/m <sup>2</sup> )	32 ± 10	33 ± 9	NS
Albumin (g/dL)	1.9 ± 0.5	2.1 ± 0.8	NS
(g/L)	19 ± 5	21 ± 8	
Prealbumin (mg/dL)	9.7 ± 4.4	9.8 ± 4.0	NS
(mg/L)	97 ± 44	98 ± 40	
WBC count (cells/mm <sup>3</sup> )	12.9 ± 6.7	13.9 ± 4.6	NS
Serum creatinine (mg/dL)	1.2 ± 0.5	3.2 ± 1.8	0.001
(μmol/L)	106 ± 44	283 ± 159	
Predicted CrCl (mL/min)	73 ± 34	36 ± 20	0.001
PN/EN (n/n)	16/24	5/16	NS
PN/EN duration (d)	39 ± 53	31 ± 22	NS
Sepsis (n)	14 (35%)	12 (57%)	NS
ISS	33 ± 10	31 ± 13	NS

ICU length of stay (d)	36 ± 37	27 ± 14	NS
Hospital length of stay (d)	45 ± 38	38 ± 26	NS
Survival (lived/died, n/n)	22/18	17/4	NS

BMI, body mass index; CrCl, creatinine clearance; DM, diabetes mellitus; EN, enteral nutrition; GSW, gun shot wound; ICU, intensive care unit; ISS, injury severity score; MVA, motor vehicle accident; NS, not significant; PN, parenteral nutrition; WBC, white blood cell

**Table 3** Response to continuous intravenous infusion therapy: Trauma patients without renal failure (RF) versus trauma patients with RF

Variable	Without RF (n = 40)	With RF (n = 21)	P
Hospital day infusion initiated (d)	7.6 ± 7.8	8.5 ± 7.0	NS
Day post initiation of PN/EN (d)	4.4 ± 5.5	5.0 ± 7.2	NS
Duration of insulin infusion (d)	11.9 ± 12.1	9.2 ± 4.9	NS
Average amount of insulin received (units/d)	93 ± 43	105 ± 40	NS
Average carbohydrate intake (g/d)	163 ± 81	161 ± 97	NS
Hrs to achieve BG 70 - 149 mg/dL 3.9 - 8.3 mmol/L	5.0 ± 3.0	6.1 ± 3.3	NS
BG during insulin infusion (mg/dL)	122 ± 15	133 ± 14	0.01
Hrs/d BG 70 - 149 mg/dL 3.9 - 8.3 mmol/L	19.6 ± 4.7	16.1 ± 3.3	0.001
Hrs/d BG > 149 mg/dL > 8.3 mmol/L	3.4 ± 3.0	6.9 ± 3.2	0.001
Hrs/d BG < 70 mg/dL < 3.9 mmol/L	0.7 ± 0.8	1.4 ± 1.1	0.01
BG < 60 mg/dL (n, %) < 3.3 mmol/L	14 (35%)	16 (76%)	0.005
BG < 40 mg/dL (n, %) < 2.2 mmol/L	0 (0%)	6 (29%)	0.001

BG, blood glucose concentration; EN, enteral nutrition; Hrs, hours; n, number of patients;

NS, not significant; PN, parenteral nutrition

**Table 4** Characteristics of patients with renal failure who developed severe hypoglycemia

Variable	With Severe Hypoglycemia (n = 6)	Without Severe Hypoglycemia (n = 15)	P
Age (yrs)	69 ± 17	56 ± 16	NS
Weight (kg)	90 ± 22	104 ± 32	NS
Albumin (g/dL)	1.9 ± 0.7	2.1 ± 0.9	NS
(g/L)	19 ± 7	21 ± 9	
Prealbumin (mg/dL)	10.6 ± 4.7	9.5 ± 3.8	NS
(mg/L)	106 ± 47	95 ± 38	
WBC count (cells/mm <sup>3</sup> )	12.7 ± 2.9	14.5 ± 5.1	NS
Serum creatinine (mg/dL)	2.8 ± 0.9	3.3 ± 2.1	NS
(μmol/L)	248 ± 80	292 ± 186	
Received hemodialysis (n,%)	2 (33%)	6 (40%)	NS
History of DM (n, %)	4 (67%)	7 (47%)	NS
Days of RHI infusion (d)	8 ± 4	10 ± 5	NS
Sepsis (n, %)	4 (66%)	8 (53%)	NS
ISS	26 ± 9	28 ± 14	NS
Hospital length of stay (d)	36 ± 18	39 ± 29	NS
Survival (lived/died, n/n)	6/0	11/5	NS
Average BG (mg/dL)	137 ± 16	131 ± 13	NS
(mmol/L)	7.6 ± 0.9	7.3 ± 0.7	
Average RHI intake (units/d)	100 ± 52	107 ± 36	NS
Average CHO intake (g/d)	157 ± 106	163 ± 97	NS

BG, blood glucose concentration; CHO, carbohydrate; DM, diabetes mellitus; ISS, injury severity score; RHI, regular human insulin; WBC, white blood cell

**Table 5** Reported incidence of severe hypoglycemia and renal failure from the major trials

Trial	Prevalence of	
	Renal Failure	Severe Hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L)
Leuven 1[3]	Four patients with dialysis prior to ICU admission	5.1%
Leuven 2[31]	6.2% prior to ICU admission 20% with AKI	18.7%
NICE-Sugar[2]	35% with “renal dysfunction” 15.4% received CRRT	6.8%
WISEP[29]	31.1% with AKI	17.0%
Glucontrol[30]	523 days of CRRT	8.7%

AKI, acute kidney injury; BG, blood glucose; CRRT, continuous renal replacement therapy; ICU, intensive care unit

Figure 1. Blood glucose response to continuous intravenous insulin infusion therapy for patients without renal failure (without RF) versus patients with renal failure (With RF). Blood glucose concentration (mmol/L) = 0.0551 X blood glucose concentration (mg/dL). NS, not significant. \*denotes significant ( $p < 0.05$ ) pair-wise differences between groups.

