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# Total parenteral nutrition–associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants

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## Index words:

Hyperglycemia;  
Hospital length of stay;  
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Overfeeding

## Abstract

**Purpose:** We studied the effects of total parenteral nutrition (TPN) associated hyperglycemia on the clinical outcome in premature septic infants in the neonatal intensive care unit.

**Methods:** The charts of all premature infants weighing less than 1500 g upon admission to the neonatal intensive care unit between January 1, 2002, and December 31, 2002, with sepsis, ventilator dependence, and feeding intolerance were studied. Maximum serum glucose concentrations were compared with duration of TPN, mechanical ventilation, hospital length of stay, and survival using Pearson regression analysis and Student's *t* test.

**Results:** Thirty-seven patients met the search criteria. The average caloric intake for all infants at the time of blood culture–proven sepsis was  $83 \pm 19$  kcal/kg per day. The maximum serum glucose concentration (milligrams per deciliter) after having positive blood cultures (sepsis) was positively correlated with the duration of TPN ( $r = 0.45$ ,  $P = .005$ ), length of dependence on mechanical ventilation ( $r = 0.45$ ,  $P = .006$ ), and hospital length of stay ( $r = 0.36$ ,  $P = .03$ ). The average maximum serum glucose level was significantly higher in the nonsurviving infants ( $241 \pm 46$  vs  $141 \pm 48$ ,  $P < .0001$ ).

**Conclusion:** Hyperglycemia correlated with prolonged ventilator dependency and increased hospital length of stay in premature septic infants. Avoidance of excessive nutrient delivery and tight glycemic control during periods of acute metabolic stress may improve outcome in this patient population.

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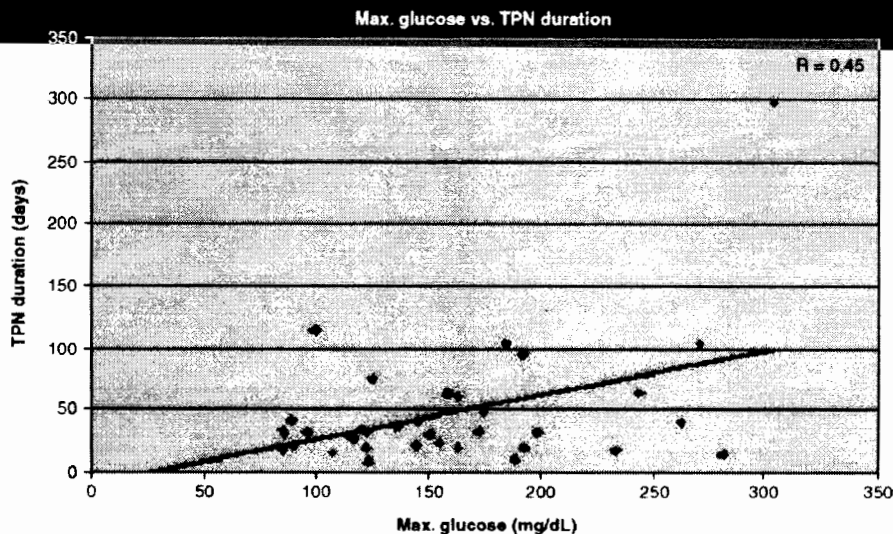
Most preterm infants are dependent on total parenteral nutrition (TPN) to prevent hypoglycemia and provide a sufficient energy intake. However, diminished tolerance for

parenteral glucose delivered at high rates frequently provokes hyperglycemia in this patient population [1]. This diminished tolerance is further exacerbated in the presence of infection, which impairs hepatic glucose uptake and enhances insulin resistance [2]. Several studies have clearly identified the association between hyperglycemia and increased morbidity and mortality in the critically ill adult patient population [3,4]. The aim of this study was to

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**Fig. 1** Maximum serum glucose concentrations correlate directly ( $R = 0.45$ ,  $P = .005$ ) with duration of TPN.

identify the correlation between TPN-associated hyperglycemia and clinical outcome in premature septic infants in the neonatal intensive care unit (NICU).

## 1. Methods

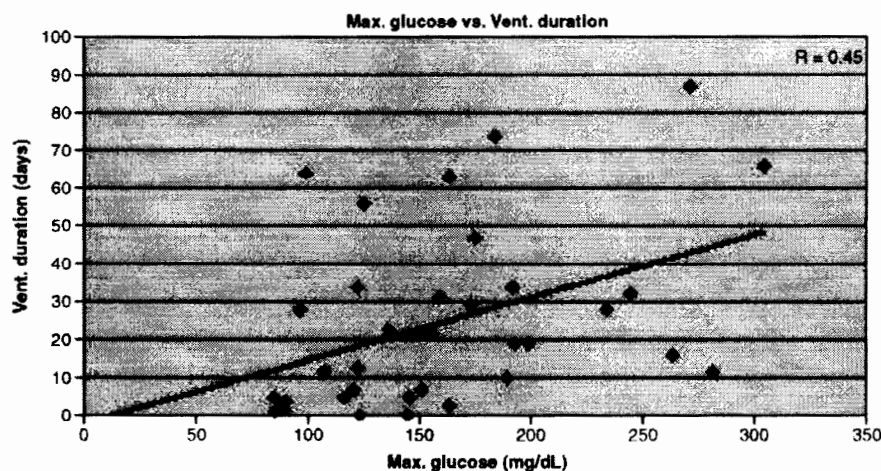
The study was approved by the institutional review boards at the University Hospitals of Cleveland and the Rainbow Babies and Children's Hospital. All ventilator-dependent premature infants weighing less than 1500 g with culture-proven sepsis requiring TPN who were treated at Rainbow Babies and Children's Hospital's NICU between January 1, 2002, and December 31, 2002, were identified from a prospectively maintained database. Prematurity was defined as gestational age of less than 37 weeks, and sepsis was confirmed by the positive growth of microorganisms in 2 or

more isolated blood culture samples. Hyperglycemia was defined as a serum glucose level of more than 120 mg/dL.

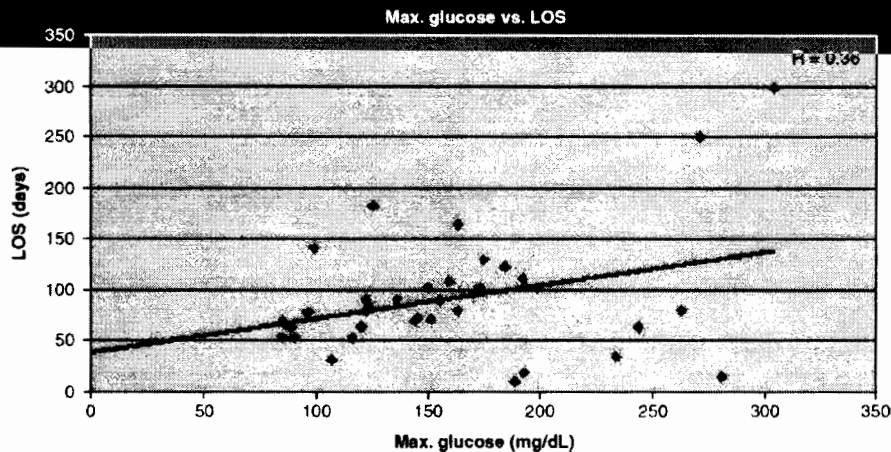
Data obtained from the database and from a retrospective review of the patients' medical records included: gestational age, weight, blood culture results, maximum glucose levels within 1 week after blood culture-proven sepsis, caloric intake based on TPN administration, duration of TPN, duration of mechanical ventilation, hospital length of stay, clinical complications, and discharge status. Pearson regression analysis and Student's  $t$  test were used in statistical analysis, and a  $P$  value of less than .05 was considered significant.

## 2. Results

Thirty-seven patients who met the study criteria were identified from the database. The average gestational age was 26 weeks (range, 23-34 weeks). The most common organism



**Fig. 2** Maximum serum glucose concentrations correlate directly ( $R = 0.45$ ,  $P = .006$ ) with duration of mechanical ventilation. Vent indicates ventilation.



**Fig. 3** Maximum serum glucose concentrations correlate directly ( $R = 0.36$ ,  $P = .03$ ) with hospital length of stay. LOS indicates length of stay.

isolated from the blood cultures was coagulase-negative staphylococci in 76% of the patients. Exclusive of acute respiratory distress syndrome of prematurity and sepsis, there were 14 (38%) patients who had other significant complications (5 with necrotizing enterocolitis, 8 with intraventricular cerebral hemorrhage, and 1 patient with both intraventricular cerebral hemorrhage and pulmonary hemorrhage). The overall mortality was 16% ( $n = 6$ ). The average caloric intake for all infants during the first week after the blood culture-proven sepsis was  $83 \pm 19$  kcal/kg per day. The maximum serum glucose concentration (milligrams per deciliter) while in the NICU and after having positive blood cultures was positively correlated with the duration of TPN ( $r = 0.45$ ,  $P = .005$ ) (Fig. 1), length of dependence on mechanical ventilation ( $r = 0.45$ ,  $P = .006$ ) (Fig. 2), and hospital length of stay ( $r = 0.36$ ,  $P = .03$ ) (Fig. 3). In addition, the hospital length of stay was significantly longer in surviving infants with maximum serum glucose levels of more than 120 mg/dL ( $P = .006$ ) (Fig. 4). Furthermore, the

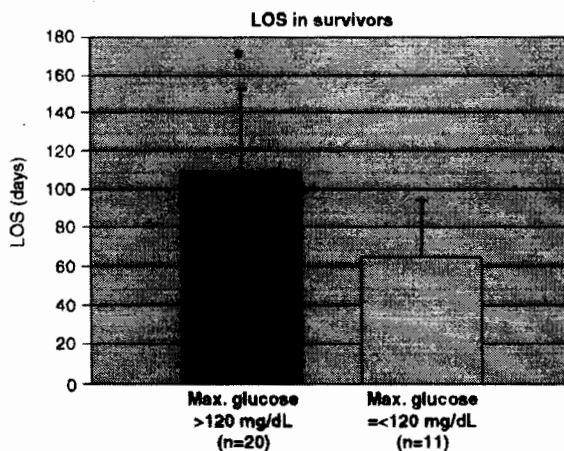
average maximum serum glucose level was significantly higher in the nonsurviving infants ( $241 \pm 46$  vs  $141 \pm 47$ ,  $P < .0001$ ) (Fig. 5).

### 3. Discussion

Survival has increased significantly in premature infants. This survival is, in large part, secondary to the use of TPN in this patient population, especially in the very low-birth-weight (<1500 g) infants, whose gut function is insufficiently mature to tolerate adequate enteral nutrition. However, hyperglycemia and increased incidence of infection are considered major risks associated with the use of TPN [5-9]. Our study shows that the effects of TPN-associated hyperglycemia in septic very low-birth-weight infants was significantly related to morbidity and mortality.

Hyperglycemia has been directly associated with immunocompromise. Cellular glucose overload in the critically ill hyperglycemic patient may be responsible for mitochondrial dysfunction [10]. Deficiencies in white blood cell activation and function, including impaired granulocyte adhesion, chemotaxis, and phagocytosis; decreased respiratory burst; and impaired intracellular killing, as well as decreased immunoglobulin function and complement fixation, have all been demonstrated in vitro in the presence of hyperglycemia and have been shown to improve with glucose control [7,11].

Hyperglycemia has been associated with an increased risk for infection-related morbidity and increased mortality in adult trauma, postoperative, and intensive care unit patients receiving excess calories [8,9,12]. These findings are further supported by the significant relationship between maximum serum glucose concentration and increased morbidity and mortality in our septic infant population. Similar findings have also been observed in a recent retrospective study of infants with necrotizing enterocolitis [13].



**Fig. 4** Comparison of hospital length of stay between survivors based on maximum serum glucose concentrations.  $*P = .006$ .

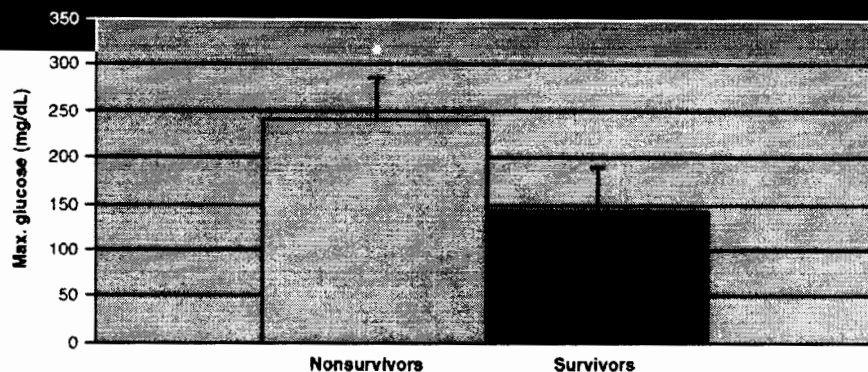


Fig. 5 Comparison of average maximum serum glucose concentrations between survivors and nonsurvivors. \* $P < .0001$ .

During acute injury states, there are 2 major contributors to hyperglycemia. One is the acute metabolic stress response itself. Tissue injury such as sepsis induces a cascade of metabolic events, which begins with the synthesis and secretion of cytokines followed by the cytokine-induced elaboration of counterregulatory hormones. Among these hormones are glucagon and epinephrine (which increase blood glucose concentration by inducing hepatic glycogenolysis, increasing Cori cycle glucose production and suppressing pancreatic insulin production in response to elevated blood glucose levels) and cortisol (which promotes gluconeogenesis). Acute metabolic stress is also characterized by the development of insulin resistance, where the ability of insulin to effect glucose deposition into storage tissue is diminished. These mechanisms are important promoters of hyperglycemia during acute injury states.

The second cause of hyperglycemia is excess caloric administration, particularly during parenteral nutrition delivery [5]. Overfeeding can be particularly harmful in catabolic states where excess calories cannot be effectively deposited into storage tissue because of insulin (and growth hormone) resistance.

In this retrospective study, it is not possible to determine to what extent each of these 2 mechanisms contributed to hyperglycemia. Measurement of the magnitude and duration of the acute metabolic stress response and comparing indirect caloric measurement of energy expenditure with actual caloric intake would help answer this question. The magnitude of the acute metabolic stress response has been quantified in critically ill infants by measuring the serum concentration of the acute phase reactant C-reactive protein (CRP), and furthermore, changes in injury-induced CRP values have been shown to coincide with similar alterations in energy expenditure in this patient population [14,15]. Serum CRP concentrations have also been shown to have a predictive outcome significance in mortality, morbidity, and hospital length of stay [16,17].

Premature infants develop hyperglycemia when receiving TPN despite a rate of glucose infusion that matches their basal requirements (4-7 mg/kg per minute) [18]. This phenomenon may be because of the fact that immature

babies are unable to secrete insulin in appropriate amounts and are relatively resistant to insulin and their pancreatic beta cell secretion is impaired in hyperglycemic conditions [19,20]. In addition, by inducing the acute metabolic stress response, sepsis impairs hepatic glucose uptake [2], enhances insulin resistance, and increases hepatic glycogenolysis, further increasing the incidence, duration, and magnitude of hyperglycemia.

The premature infant who is not growing, not septic, and not unduly stressed requires an energy intake of about 40 to 50 kcal/kg per day for basal energy expenditure [21,22]. During periods of acute metabolic stress (ie, sepsis), a catabolic state exists and somatic growth cannot occur. Furthermore, septic infants are typically cared for in an intensive care environment (as was the case for all of the infants in the present study) where activity-related energy requirements and insensible energy losses are greatly reduced relative to age- and weight-matched healthy normally active infants in a normal (nonthermoregulated) environment. These facts substantially reduce the total energy expenditure (therefore, the amount of calories necessary for nutritional support) in this patient population. It has been shown that even during periods of severe acute metabolic stress, the increase in daily measured energy expenditure does not usually exceed 60 kcal/kg per day [14]. During acute injury states, caloric repletion should not exceed measured energy expenditure to avoid overfeeding. If indirect calorimetry assessment is not available, caloric delivery should not exceed basal energy expenditure values until the catabolic injury response period resolves [23]. Because the infants in the present study population had an average caloric intake of 83 kcal/kg per day during the first week after having positive blood cultures, a period in which septic infants in a neonatal intensive care setting have demonstrated an acute metabolic stress response [24], it is likely that this amount of caloric delivery substantially exceeds metabolic demands.

In addition to promoting immunocompromise, caloric overfeeding can have a significant negative effect on respiration because of increased carbon dioxide production [15,25]. Premature neonates have a substantially decreased

pulmonary reserve and inadequate ability to eliminate increased amounts of carbon dioxide, which can prolong ventilator dependency. Thus, caloric overfeeding, in addition to acute metabolic stress (ie, sepsis), may have accounted for increased hyperglycemia and mechanical ventilator dependency in our septic infant population.

It has been clearly shown that tight glycemic control with intravenous insulin improves morbidity and mortality in the adult diabetic and nondiabetic population during periods of critical illness [26-28]. It is speculated that the tight glycemic control rather than the administration of insulin per se that has a beneficial effect in the critically ill persons [4,10]. Insulin infusion has been shown to be efficacious in maintaining euglycemia in the premature neonate [29].

In conclusion, our study shows that hyperglycemia in the premature septic infant correlates with increased morbidity, mortality, and hospital length of stay. On the basis of these data and recent reports in critically ill adult patients, we propose that avoiding caloric overfeeding, perhaps in conjunction with careful and appropriately monitored insulin administration, to limit hyperglycemia during acute injury states in critically ill infants may be effective in reducing hyperglycemia-associated morbidity and mortality.

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## Discussion

*Doctor (moderator):* I thought this was a wonderful paper and I hope the importance of it really gets carried out into the literature and is really perceived, because I think it is one of the first where the neonatal population has really been shown to have that same correlative role as the Vanderberg study in adults.

You did a univariate analysis in terms of your looking at these outcomes. Did you try to control for other comorbidities in some of these patients that might

also influence mortality, and do sort of a multivariate regression analysis. Would that tighten up or strength perhaps the results?

*Diya Alaedeen, MD (response):* We conducted a univariate logistic regression analysis looking at hyperglycemia as it relates to morbidity in these patients. We had

14 patients with complications: 5 with necrotizing enterocolitis, 8 with intraventricular hemorrhage, and 1 with pulmonary hemorrhage and intraventricular hemorrhage. We found that hyperglycemia is a significant predictor for complications in this patient population. However, our statistics had insufficient power. A larger prospective study can better validate this finding.