Pediatr Cardiol
DOI 10.1007/s00246-009-9512-4

ORIGINAL ARTICLE

Glycemic Control for Postoperative Pediatric Cardiac Patients

Catherine M. Preissig · Mark R. Rigby · Kevin O. Maher

Received: 22 May 2009 / Accepted: 30 July 2009

Abstract This study aimed to determine the prevalence of hyperglycemia among pediatric postoperative cardiac patients, its impact on outcomes, and whether hyperglycemia can be controlled effectively in this population. A retrospective chart review of 100 postoperative patients admitted to the authors' pediatric cardiac intensive care unit (ICU) was conducted. Patients were evaluated for incidence of hyperglycemia, defined as blood glucose (BG) level exceeding 7.7 mmol/l (140 mg/dl), and outcomes. The evaluation also included 20 different postoperative patients with a BG level exceeding 7.7 mmol/l (140 mg/dl) who received management with insulin via the authors' pediatric-specific glycemic control protocol. The BG control and hypoglycemic rates in this cohort were assessed. The prevalence of hyperglycemia was 84%. The hyperglycemic patients had higher inotrope scores, longer hospital stays, more mechanical ventilation days, and higher mortality rates than those without hyperglycemia. For the patients with hyperglycemia managed via the authors' pediatric-specific glycemic control protocol, 62% of all BG values were within the authors' goal range, and less than 4% of BG values were less than 3.3 mmol/l (60 mg/dl). No patient had a BG level lower than 2.2 mmol/l (40 mg/dl) during glycemic management. Severe hyperglycemia is prevalent among postoperative pediatric cardiac patients and correlates with morbidity and mortality. Hyperglycemia may be controlled effectively in these patients using a pediatric-specific glycemic control protocol without increasing the incidence of hypoglycemia.

Keywords Hyperglycemia · Intensive care · Outcomes · Pediatrics · Postoperative care

C. M. Preissig (✉) · M. R. Rigby
Department of Pediatrics, Division of Critical Care Medicine, Emory University School of Medicine, 1405 Clifton Rd NE, Atlanta, GA 30322, USA
e-mail: catherine.preissig@choa.org

C. M. Preissig · M. R. Rigby · K. O. Maher
Children's Healthcare of Atlanta, Atlanta, GA 30322, USA

K. O. Maher
Department of Pediatrics, Division of Pediatric Cardiology, Emory University School of Medicine, Atlanta, GA 30322, USA

Hyperglycemia experienced by critically ill adults is associated with increased morbidity and mortality, and tight glycemic control with insulin may improve outcomes in some patient settings [11, 15, 18, 20, 22, 25]. Questions regarding the safety and efficacy of this therapy, the extent of outcome improvement, the goal blood glucose (BG) range, and the target patient population for treatment are of significant debate [3, 7, 13, 31, 32, 35]. However, despite conflicting literature on glycemic control, several medical advisory committees recommend the aforementioned treatment as standard care for adults [14, 28, 30].

Studies in pediatrics demonstrate that critical illness hyperglycemia (CIH) is prevalent and strongly associated with increased morbidity and mortality in medical, neurotrauma, surgical, and cardiac populations, yet definitive outcome trials in pediatric intensive care units (ICUs) have not been conducted to date [2, 6, 10, 19, 29, 37, 39]. Recently, Vlasselaers et al. [34] reported findings from the first glycemic control outcome trial conducted in children. In their trial of 700 pediatric subjects, 75% were postoperative pediatric cardiac ICU patients. This trial found decreased mortality, shorter ICU length of stay, and decreased markers of inflammation in patients treated with

Published online: 25 August 2009

insulin to maintain fasting BG levels, suggesting this intervention may improve outcomes for children. Of significant concern in this trial, however, was the finding that approximately 25% of the children undergoing strict glycemic control showed severe rates of hypoglycemia.

No published study to date has demonstrated safe, effective management of CIH in postoperative pediatric cardiac ICU patients. Given the potential outcome improvements with the glycemic control suggested by Vlasselaers et al. [34] for this population, demonstration of safe hyperglycemia management for pediatric cardiac patients is not only warranted but may be crucial. We report an extremely high incidence of CIH and associated worse outcome among pediatric cardiac ICU patients postoperatively and our experience controlling hyperglycemia using a pediatric-specific management protocol.

Materials and Methods

The Pediatric Cardiac ICU at Children's Healthcare of Atlanta is a 27-bed dedicated unit that cares for infants and children with congenital and acquired heart disease. We retrospectively reviewed 100 charts of postoperative patients admitted to the pediatric cardiac ICU between April and June 2008 to assess for the incidence of hyperglycemia and outcome parameters including ICU length of stay (LOS), ventilator days, bloodstream infections, and mortality. The 100 patients were randomly selected from 223 patients admitted to the ICU during that time. Hyperglycemia was defined as a BG level exceeding 7.7 mmol/l (140 mg/dl) on two or more occasions at any time during the ICU stay, as assessed by routine laboratory or bedside point-of-care procedures.

All the reviewed patients had at least two BG values available for analysis. During their ICU course, 15 patients received either intravenous or subcutaneous insulin treatment (Novalin R, Novo Nordisk Pharmaceuticals, Inc, Princeton, NJ) for hyperglycemia, but only six of these patients were treated consistently to maintain BG in a goal target range. Surgical procedure was coded by the Risk Adjusted Classification for Congenital Heart Surgery (RACHS-1) [17]. We quantified peak inotrope requirement during the ICU stay using the published inotrope score by Wernovsky et al. [36].

We further reviewed 20 consecutive postoperative pediatric cardiac ICU patients admitted between October and June 2008 with hyperglycemia who received insulin treatment by a previously published, standardized pediatric-specific protocol developed at our institution and used in the pediatric cardiac ICU at the physician's discretion [26]. Patients receiving this protocol were screened for hyperglycemia via twice-daily BG monitoring. Insulin infusion was initiated for patients with two consecutive BG levels exceeding 7.7 mmol/l (140 mg/dl) 1 h apart. These patients were titrated to maintain a BG level of 4.4–7.7 mmol/l (80–140 mg/dl).

We evaluated patients in our pediatric cardiac ICU receiving the aforementioned glycemic management for efficacy of glucose control and associated adverse events, including hypoglycemia. We excluded patients in this cohort who overlapped with the 100 patients evaluated for hyperglycemia. All aspects of this study met institutional review board approval.

Blood glucose levels were compared using Student's two-tailed t tests, and a P value less than 0.05 was considered statistically significant. Other results in different groups were compared using the Student's t test for normally distributed data, the Mann–Whitney U test for non-normally distributed data, and the chi square test for comparison of proportions. Statistical testing was performed using SPSS 15.0, (Chicago, IL, USA).

Results

Incidence of Hyperglycemia and Outcomes

For this study, 4,173 BG values (laboratory or bedside point-of-care results) were available for analysis. Of 100 patients, 84 had at least two BG levels exceeding 7.7 mmol/l (140 mg/dl) and thus met our definition of hyperglycemia. There were no significant differences in weight, gender, or ethnicity in the patients with and those without CIH (Table 1). The average age was 3.2 years for the patients as a whole, 2.8 years for those with CIH, and 5.4 years for those without CIH.

All the patients in our study required mechanical ventilation. The patients with CIH were more likely to require support measures such as continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), or both compared to those without CIH. A significantly greater number of patients with CIH required vasopressors or inotropes (including dopamine, dobutamine, epinephrine, norepinephrine, or milrinone) and received steroids than those without CIH ($P < 0.05$). The patients with CIH had significantly higher inotrope scores (3.74 ± 2.9) and RACHS-1 scores (4.3 ± 1.1) than those without CIH (0.79 ± 1.6 and 2.05 ± 0.4, respectively) ($P < 0.05$) (Table 1).

Table 2 represents peak BG levels and outcomes for all the patients. Most of the patients (84%) experienced CIH. The peak BG was 13.2 ± 3.3 mmol/l (240 ± 66 mg/dl) for the patients as a whole, 14.6 ± 4.5 mmol/l (266 ± 82 mg/dl) for those with CIH, and 5.8 ± 2.3 mmol/l (106 ± 43 mg/dl) for those without CIH. Of 84 patients

Table 1 Baseline characteristics in post-operative pediatric cardiac ICU patients

	All patients ($n = 100$)	+CIH ($n = 84$)	−CIH ($n = 16$)
Male gender, *n* (%)	42 (42)	37 (44)	6 (38)
Average age in years (range)	3.2 (2 days–18 years)	2.8[a] (2 days–14 years)	5.4 (5 days–18 years)
Average weight in kg (range)	14.4 (2–75.2)	13.3 (2–39.4)	20 (2.5–75.2)
Pressors/inotropes, *n* (%)	64 (64)	61 (73)[a]	3 (18)
Steroids, *n* (%)	33 (33)	30 (36)[a]	3 (18)
CRRT, *n* (%)	4 (4)	4 (4.7)	0 (0)
ECMO, *n* (%)	8 (8)	8 (9.5)	0 (0)
Surgery without CPB, *n* (%)	31 (31)	22 (26)	9 (56)
Surgery with CPB, *n* (%)	69 (69)	62 (74)[a]	7 (44)
Peak inotrope score	3.1 ± 2.8	3.74 ± 2.9[a]	0.79 ± 1.6
RACHS-1	3.2 ± 0.9	4.3 ± 1.1[a]	2.05 ± 0.4

CIH critical illness hyperglycemia, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *RACHS-1* risk adjusted classification for congenital heartsurgery, *CPB* cardiopulmonary bypass

[a] Denotes $P < 0.05$ compared to patients without CIH

Table 2 Peak blood glucose levels and outcomes

	All patients ($N = 100$)	+CIH ($N = 84$)	−CIH ($N = 16$)
Peak BG (mmol/l)	13.2 ± 3.3	14.6 ± 4.5[a]	5.8 ± 2.3
Average CICU LOS in days (range)	6 (0.8–52)	7[a] (0.6–52)	2.5 (0.8–7)
Average MV days (range)	3.8 (0.2–45)	4[a] (2–45)	1.5 (0.2–4)
BSIs, *n* (%)	3 (3)	3 (4)	0 (0)
Deaths, *n* (%)	5 (5)	5 (6)	0 (0)

CIH critical illness hyperglycemia, *BG* blood glucose, *LOS* length of stay, *BSI* blood stream infection, *MV* mechanical ventilator

[a] Denotes $P < 0.05$ compared to patients without CIH

with CIH, 9 (10.7%) had a BG level lower than 3.3 mmol/l (60 mg/dl) and 6 (7%) had a BG level lower than 2.2 mmol/l (40 mg/dl). The patients with CIH had a longer mechanical ventilation time (4 vs. 1.5 days; $P < 0.05$), a higher rate of bloodstream infections (3 vs. 0), a higher death rate (5 vs. 0), and a longer ICU LOS (7 vs. 2.5 days; $P < 0.05$) than those without CIH.

We further evaluated risk for the development of hyperglycemia based on support measures and illness severity indicators (Fig. 1). Patients requiring steroids, vasopressors or inotropes, CRRT, or ECMO had the highest risk for CIH, with CIH developing in 90% of those receiving steroids, 95% of those requiring vasopressors, and 100% of those requiring either CRRT or ECMO, albeit notwithstanding other support measures.

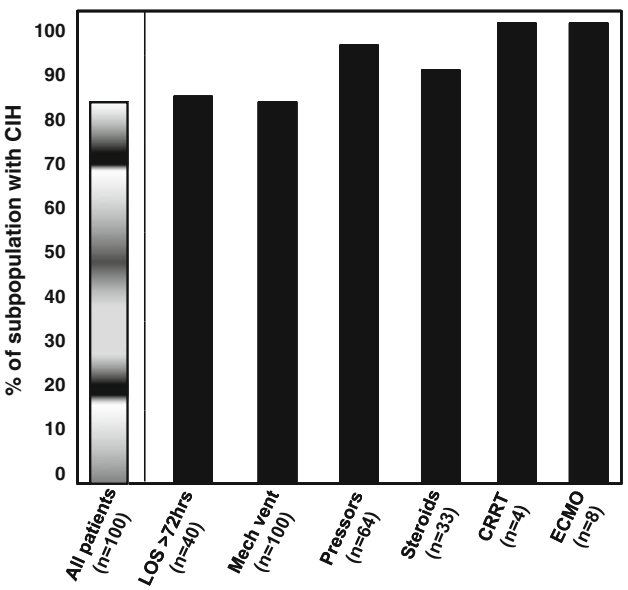

Fig. 1 Incidence and risk factors of hyperglycemia in postoperative pediatric cardiac patients. LOS, length of stay; Mech vent, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation

Glycemic Control Using a Pediatric-Specific Protocol

Patients with hyperglycemia in our pediatric cardiac ICU can be placed on a pediatric-specific glucose control protocol at the physician's discretion. A total of 20 patients

Table 3 Baseline characteristics of patients receiving glycemic control via our pediatric-specific protocol

	All patients ($n = 20$)
Male gender, *n* (%)	9 (45)
Average age in years (range)	4.1 (2 days–6 years)
Average weight in kg (range)	19 (2.2–41)
Peak BG (mmol/l)	16.6 ± 3.2
Average CICU LOS in days (range)	5.8 (0.4–23)
Average MV days (range)	4.4 (2–19)

BG blood glucose, *LOS* length of stay, *MV* mechanical ventilator

placed on this protocol in the pediatric cardiac ICU were evaluated for the efficacy of glycemic control, defined as the percentage of BG levels maintained within our target range of 4.4–7.7 mmol/l (80–140 mg/dl), and safety, based on the number of hypoglycemic episodes. The baseline characteristics of these patients are presented in Table 3. The average BG level prompting insulin treatment among these patients was 16.6 mmol/l (302 mg/dl) (Table 4). The average time required to reach the target of a BG level lower than 7.7 mmol/l (140 mg/dl) was 3.2 h. The patients with hyperglycemia required glycemic control with insulin for 4.6 days (range 3–11 days) and an average insulin infusion of 0.09 units/kg/h to maintain a BG level within our target range of 4.4 to 7.7 mmol/l (80–140 mg/dl). Two patients (10%) had a single BG level lower than 3.3 mmol/l (60 mg/dl) during treatment, and no patient receiving our protocol had a BG level lower than 2.2 mmol/l (40 mg/dl) (Table 4).

Figure 2 demonstrates how well BG levels were maintained at or near the goal BG ranges. Less than 4% of all BG values were lower than 3.3 mmol/l (60 mg/dl). During glycemic management, 62% of all BG values were within 4.4–7.7 mmol/l (80–140 mg/dl), and 80% of all values were less than 8.8 mmol/l (160 mg/dl). Only 12% of BG values exceeded 9.9 mmol/l (180 mg/dl), and less than 3% exceeded 11 mmol/l (200 mg/dl).

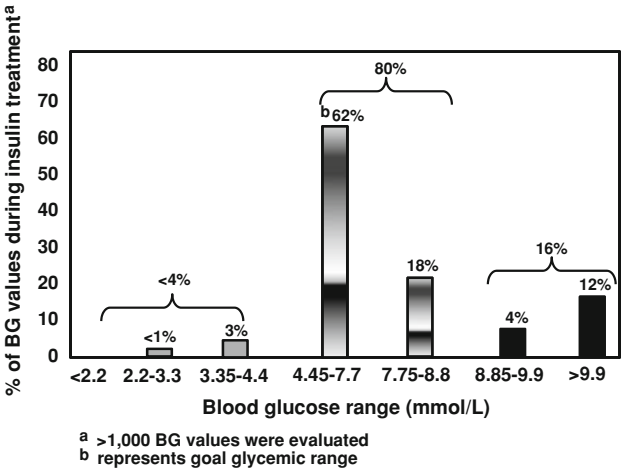

Fig. 2 Glycemic control in postoperative pediatric cardiac intensive care unit (ICU) patients managed via our protocol. More than 60% of all BG values were within our goal glycemic range of 4.45 to 7.7 mmol/l (80–140 mg/dl) during management with insulin via our protocol. BG, blood glucose

Discussion

The findings in this study emphasize the high incidence of hyperglycemia and its association with poor outcomes. This report is the first to describe an approach to the management of hyperglycemia in infants and children after cardiac surgery without high rates of hypoglycemia. To our knowledge, the only studies to date that specifically evaluated hyperglycemia in postoperative pediatric cardiac ICU patients were those conducted by Yates et al. [38] in 2006, and by Falcao et al. [9] 2007. Yates and colleagues reviewed 184 pediatric patients younger than 12 months undergoing cardiac surgery that required cardiopulmonary bypass, evaluating them for hyperglycemia, defined as a BG level higher than 6.9 mmol/l (126 mg/dl), and outcome association. They did not specifically report the incidence of hyperglycemia in their study population, but did find an association of initial BG, peak BG, and duration of hyperglycemia with morbidity and mortality [31]. Falcao and colleagues recently reviewed a broader cohort of postoperative cardiac patients, including both older children and those not requiring cardiopulmonary bypass, and reported a high incidence of hyperglycemia (78% of patients with at least 1 BG level exceeding 11 mmol/l [200 mg/dl]) as well as an associated increase in morbidity and mortality [9].

Table 4 Safety and efficacy of glycemic control for 20 critical illness hyperglycemia (CIH) patients managed via our protocol

Characteristic	Data
1. Average BG prompting insulin treatment	16.6 mmol/l (range: 9.2–21 mmol/l)
2. Average time to reach target BG of <7.7 mmol/l	3.2 h (range: 1–11 h)
3. Average days patients require insulin treatment to maintain glycemic control	4.6 days (range: 3–11 days)
4. Average amount of insulin required to maintain glycemic control	0.09 units/kg/h (2.16 units/kg/day)
5. Patients on insulin with BG level <3.3 mmol/l at any time during admission	10% ($n = 2$)
6. Patients on insulin with BG level <2.2 mmol/l at any time during admission	0%

Similar to Falcao et al. [9], we report an extremely high incidence of CIH (84%) among postoperative pediatric cardiac ICU patients. We have likewise been able to identify populations at risk for hyperglycemia, including those requiring mechanical ventilation, steroids, vasopressors or inotropes, CRRT, or ECMO. These findings are consistent with previously reported data from our medical/surgical pediatric ICU, in which 65% of patients requiring mechanical ventilation, 90% of those requiring vasopressor infusions, and 93% of those needing both interventions experienced persistent BG levels exceeding 7.7 mmol/l (140 mg/dl) [26].

In critically ill patients, a high BG level often is considered a form of "stress" hyperglycemia resulting from endogenous counterregulatory hormones, but other factors likely contribute to the condition, differentiating it from a pure sympathoadrenal response [1, 27, 33]. The role of necessary therapies such as catecholamines and steroids in iatrogenic hyperglycemia has not been entirely delineated. Like Yates et al. [38], we did find a statistically significant difference in vasopressor scores between patients with and those without CIH. In contrast to these authors, however, we often administer steroids to patients before surgeries requiring cardiopulmonary bypass, and occasionally for other clinical indications. In this study, 35% of the patients with CIH received steroids compared with 18.7% of those without CIH. Further studies are needed to define the exact contribution such therapeutic interventions have on CIH and implications regarding glycemic control and outcome.

Similar to the studies by both Yates et al. [38] and Falcao et al. [9] as well as other studies conducted with multiple pediatric critically ill populations, our study found worse outcomes for patients with CIH, including increased LOS, ventilation days, bloodstream infections, and mortality. The etiology of hyperglycemia and its link to poor outcome are not well understood, but animal studies suggest that CIH decreases cardiac output, cardiac index, and stroke volume while increasing systemic vascular resistance [8]. These deleterious effects may be due in part to direct effects of glucose on myocardium, evidenced by enhanced inducible nitric oxide synthase, increased nitric oxide generation, increased superoxide production, and increased cell apoptosis [4, 5].

The mechanisms by which CIH causes organ dysfunction are not well-understood, but some adult trials have demonstrated that glycemic control with insulin can reverse or prevent some of these metabolic derangements in critical illness, particularly for adult cardiac patients. Malmberg et al. [24] published one of the original glycemic control trials in 1995, reporting that intensive insulin treatment improved the long-term prognosis for diabetic patients experiencing acute myocardial infarction (AMI). Other studies with adults have shown improved morbidity and mortality with insulin infusion in multiple cardiac settings (e.g., after AMI and after cardiopulmonary bypass grafting) [12, 23].

Recently, a groundbreaking randomized controlled trial conducted by Vlasselaers et al. [34] suggested potential outcome benefit for children treated with insulin to maintain fasting BG levels. Interestingly, although the study population consisted of those admitted to a mixed medical/surgical/cardiac ICU, 75% of the patients in their report were pediatric cardiac patients. Of concern, 25% of the patients receiving strict glycemic control experienced hypoglycemia (BG $<$ 2.2 mmol/l [40 mg/dl]) compared with 5% receiving conventional control. It is well known that hypoglycemia alone is independently associated with poor outcomes for both adults and children [21, 37]. In fact, much effort with adults has been focused on developing glycemic control protocols that effectively treat hyperglycemia without causing iatrogenic hypoglycemia. For pediatric populations, fear of hypoglycemia has been a major barrier in the practice of glycemic control for critically ill children, and most pediatric practitioners consider hypoglycemia more detrimental than hyperglycemia [16].

We provide evidence of potentially safe and effective CIH management for 20 postoperative pediatric cardiac ICU patients using a pediatric-specific protocolized approach. The patients receiving our protocol had more than 60% of all their BG values within our target range. Moreover, 80% of all their values were less than 8.8 mmol/dl (180 mg/dl), and no patient had a BG level lower than 2.2 mmol/l (40 mg/dl). Our management was expedient, yet apparently safe, requiring 3.2 h to achieve target range once insulin was initiated. Our target BG range was higher than that of Vlasselaers et al. [34], which may account in part for the discrepancy in hypoglycemic rates for our patient populations. However, our hypoglycemic rates actually are lower than those reported in many adult studies that use similar glycemic control targets. They also are comparable with or lower than the rates of spontaneous hypoglycemia in our pediatric cardiac patients not treated via this protocol. Furthermore, the ideal target range for glycemic control has yet to be established for adults or children. Targeting less strict ranges to reduce hypoglycemia may be prudent for pediatric populations.

Conclusions

With recent data suggesting that glycemic control may improve outcomes for pediatric cardiac ICU patients, demonstration of safe, effective management for this population is mandatory. We describe the first study showing that such control may be possible using a

pediatric-specific approach, although larger studies are needed for further evaluation of this approach. We further demonstrate a high incidence of CIH and an association with poor outcomes in this population. Further studies to evaluate the safety and efficacy of pediatric-specific glycemic control protocols should be conducted with larger pediatric cardiac ICU populations. Randomized controlled trials using safe, effective glycemic control protocols are needed to delineate further whether this therapy is warranted for pediatric cardiac patients, and to determine what, if any, BG goal should be targeted.

References

1. Andreelli F, Jacquier D, Troy S (2006) Molecular aspects of insulin therapy in critically ill patients. Curr Opin Clin Nutr Metab Care 9:124–130
2. Branco R, Garcia R, Piva J, Casartelli C, Seibel V, Tasker R (2005) Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med 6:470–472
3. Brunkhorst F, Engel C, Bloos F, Meier Hellman A, Ragaller M, Weiler N et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139
4. Cai L, Li W, Wang G et al (2002) Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. Diabetes 51:1938–1948
5. Ceriello A, Quagliaro L, D'Amico M (2002) Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. Diabetes 51:1076–1082
6. Cochran A, Scaife ER, Hansen KW, Downey EC (2003) Hyperglycemia and outcomes from pediatric traumatic brain injury. J Trauma 55:1035–1038
7. Devos P, Preisser J (2007) Current controversies around glucose control in critically ill patients. Curr Opin Clin Nutr Metab Care 10:206–209
8. DiPette DJ, Ward-Hartley KA, Jain RK (1986) Effect of glucose on systemic hemodynamics and blood flow rate in normal and tumor tissues in rats. Cancer Res 46:6299–6304
9. Falcao G, Ulate K, Kouzekanani K, Bielefeld M, Morales J, Rotta A (2007) Impact of postoperative hyperglycemia following surgical repair of congenital heart defects. Pediatr Cardiol. doi: 10.1007/s00246-007-9178-8
10. Faustino EV, Apkon M (2005) Persistent hyperglycemia in critically ill children. J Pediatr 146:30–34
11. Finney SJ, Zekveld C, Elia A, Evans TW (2003) Glucose control and mortality in critically ill patients. JAMA 290:2041–2047
12. Furnary A, Goa G, Gunkemieir G, Wu Y, Zerr K, Bookin S (2003) Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 125:1007–1021
13. Gandhi G, Nuttall G, Abel M, Mullany C, Schaff H, O'Brien P et al (2007) Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 146:233–243
14. Garber A, Moghissi E, Bransome E (2004) American College of Endocrinology position statement on inpatient diabetes and metabolic control. Endocr Pract 10(Suppl 2):4–9
15. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters P, Bobbaers H et al (2007) Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in MICU. Am J Respir Crit Care Med 175:424–425
16. Hirshberg E, Lacroix J, Sward K, Wilson D, Morris AH (2008) Blood glucose control in critically ill adults and children: a survey on stated practice. Chest 133:1328–1335
17. Jenkins KJ, Gavreau K, Newburger JW (2002) Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 123:110–118
18. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A (2005) The impact of hyperglycemia on patients with severe brain injury. J Trauma 58:47–50
19. Klein G, Hojsak J, Schmeidler J, Rapaport R (2008) Hyperglycemia and outcome in the pediatric intensive care unit. J Pediatr 153:379–384
20. Krinsley JS (2004) Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clinic Proceed 79:992–1000
21. Krinsley J (2007) Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 35:2262–2267
22. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC (2004) Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 56:1058–1062
23. Lazar H, Chipkin S, Fitzgerald C, Bao Y, Cabral H, Apstein C (2004) Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 109:1497–1502
24. Malmberg K, Efendic S, Herlitz J, Nicol P, Welin L (1995) Randomized trial of insulin glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. JACC 20:1601–1608
25. McCowen KC, Malhotra A, Bistrian BR (2001) Stress-induced hyperglycemia. Crit Care Clin 17:107–124
26. Preissig CM, Hansen I, Roerig P-L, Rigby MR (2008) A protocolized approach to identify and manage hyperglycemia in a pediatric critical care unit. Pediatr Crit Care Med 9:581–588
27. Saltiel AR, Kahn R (2001) Insulin signalling and regulation of glucose and lipid metabolism. Nature 414:799–804
28. Skyler J, Bergenstal R, Bonow R, Buse J, Deedwania P, Gale E, Howard B, Kirkman M, Kosiborod M, Reaven P, Sherwin R (2009) Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Circulation 119:351–357
29. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V (2004) Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatr Crit Care Med 5:329–336
30. Surviving Sepsis Campaign Consortium Statement (2004) Crit Care Med 32:281–283
31. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367
32. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters M, Milants I et al (2006) Intensive insulin therapy in the medical ICU. New Engl J Med 354:449–461
33. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G (2005) Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet 365:53–59
34. Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, van den Heuvel I et al (2009) Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 6736:60044-1

35. Weiner R, Weiner D, Larson R (2008) Benefits and risks of tight glucose control in critically ill adults: a metaanalysis. JAMA 300:933–944
36. Wernovsky G, Wypij D, Jonas RA (1995) Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 92:2226–2235
37. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM (2006) Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics 118:173–179
38. Yates A, Dyke P, Taeed R (2006) Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. Pediatr Crit Care Med 7:351–355
39. Yung M, Wilkins B, Norton L, Slater F (2008) Glucose control, organ failure, and mortality in pediatric intensive care. Pediatr Crit Care Med 9:147–152