A.S.P.E.N. Clinical Guidelines : Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition

Danielle Arsenault, Megan Brenn, Sendia Kim, Kathleen Gura, Charlene Compher, Edwin Simpser, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors and Mark Puder

JPEN J Parenter Enteral Nutr 2012 36: 81 originally published online 16 December 2011
DOI: 10.1177/0148607111418980

Clinical Guideline

Journal of Parenteral and Enteral Nutrition
Volume 36 Number 1
January 2012 81-95

10.1177/0148607111418980
http://jpen.sagepub.com
hosted at
http://online.sagepub.com

A.S.P.E.N. Clinical Guidelines: Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition

Danielle Arsenault, RN, MSN; Megan Brenn, RD; Sendia Kim, MD; Kathleen Gura, PharmD; Charlene Compher, PhD, RD, CNSC, LDN, FADA; Edwin Simpser, MD; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors; and Mark Puder, MD, PhD

Background

This Clinical Guideline has been developed to guide clinical practice based on the authors' assessment of current published evidence on glycemic control in the neonate (within the first month of life) receiving parenteral nutrition (PN). The neonate receiving PN is worthy of special consideration with respect to glucose control, as this population carries an elevated risk of hyper- and hypoglycemia and may be more susceptible to deleterious effects associated with these conditions.

Untreated hyper- or hypoglycemia may lead to undesirable clinical outcomes. Prolonged or symptomatic hypoglycemia may result in neurodevelopmental impairment.[1-6] Severe hyperglycemia can lead to osmotic diuresis resulting in dehydration and electrolyte imbalance. Furthermore there is some evidence to suggest that hyperglycemia in premature infants (particularly those that are very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g)) has been positively correlated with morbidity and mortality, spurring questions about more proactive measures of managing elevated blood glucose levels in this group of patients.[7-11] Thus, hyperglycemia and hypoglycemia are clinically-relevant complications that should be considered in caring for the neonate receiving PN and it is important to examine the parameters for defining, screening, treating and preventing abnormal serum glucose values in this population.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all health care settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.[12-14] A.S.P.E.N. evaluates in an ongoing process when individual Clinical Guidelines should be updated.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such Guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

Address correspondence to: Charlene Compher, PhD, RD, CNSC, LDN, FADA, University of Pennsylvania School of Nursing, Claire M. Fagin Hall, 418 Curie Boulevard, Philadelphia, PA 19104-4217; e-mail: compherc@nursing.upenn.edu.

Table 1. Evaluation of Study Quality

Randomized Control Trial Quality [15]	
Randomization	1. Was the study described as randomized?
	2. Was the randomization appropriately performed?
Blinding	3. Was the study double-blinded?
	4. Were study participants blinded?
	5. Was the investigator blinded?
Attrition	6. Was the rate of attrition specified and appropriate statistical treatment (intent-to-treat analysis) employed?
Observational Study Quality [16]	
Study Design	7. Were the data collected prospectively?
	8. How were variables measured?
Power	9. How was sample size determined?
Attrition	10. Was the rate of attrition specified and appropriate statistical treatment employed?
Bias	11. How was the study funded?

A.S.P.E.N. Clinical Guidelines has adopted concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (http://www.gradeworkinggroup.org). The GRADE working group combined the efforts of evidence analysis methodologists and clinical guidelines developers from diverse backgrounds and health organizations to develop an evaluation system that would provide a transparent process for evaluating the best available evidence and integration of the evidence with clinical knowledge and even consideration of patient priorities. These procedures provide added transparency by developing separate grades for the body of evidence and for the recommendation. The procedures listed below were adopted from the GRADE process for use with A.S.P.E.N. Clinical Guidelines with consideration of the levels of review (by internal and external content reviewers, by A.S.P.E.N. and editing expected for approval by the A.S.P.E.N. Board of Directors.

Three primary stages are involved in developing a Clinical Guideline. The first stage is development of specific clinical questions where nutrition support is a relevant mode of therapy, questions to be answered by a rigorous review of the published literature. The questions developed are specific to a life stage group (neonates, pediatrics, adults, geriatrics, pregnancy), in a defined disease-state or clinical setting, and focused on clinical outcomes associated with nutrition support therapy.

The second stage is a transparent process that describes how each research report is evaluated. Finally, a Clinical Guideline recommendation incorporates expert clinical judgment about the context of application of this research into a practice setting with consideration of the relative risks and benefits of doing so.

Pertinent published papers are obtained and appraised for evidence quality according to the schema in Tables 1 and 2.

The GRADE system combines all the references obtained for a given question into a table that is organized by clinical outcome. The criteria to be used in evaluating the quality of the evidence are summarized in Table 2. Consistency, directness, precision and risk of publication bias are important to include in the assessment of evidence quality.[17] Inconsistency of randomized controlled trial (RCT) findings means that the effect size represented by the intervention has a wide confidence interval, that the effects are conditional (one effect at baseline with a different effect at a later time point), or that some studies report a positive and others a negative finding for reasons that cannot be explained by research quality. Indirect evidence might include use of a surrogate outcome (adequate energy intake rather than measured growth in children) or data tangential for the question at hand (interpolated from evidence in another age group or compared to oral diet rather than to parenteral nutrition). Imprecision risk is high when there is no power statement to justify the sample size. The risk of publication bias is high when most of the published research reports were funded by an industry that might benefit from positive outcomes reported. Meta-analyses and systematic reviews may be used to combine the results of studies to further clarify the overall outcome of these studies but will not be considered in the grading of the Guideline to avoid considering primary research reports multiple times.

RCT evidence begins with a *high* rating and observational evidence with a *low* quality rating. The quality rating may be downgraded due to limitations in study design

Table 2. GRADE Criteria for Grading Evidence for Each Question

Type of Evidence	Initial Grade	Criteria to Decrease Grade	Criteria to Increase Grade	Final Quality Grade
RCT	High	*Study Limitations* Serious (−1) or very serious (−2) limitation to study quality	*Strong Association* Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)	High Moderate
OBS	Low	*Consistency* Important inconsistency (−1)	Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)	Low Very Low
		Directness Some (−1) or major (−2) uncertainty about directness		
		Precision Imprecise or sparse data (−1)	*Dose-response gradient* Evidence of a dose response gradient (+1)	
		Publication bias High probability of reporting bias (−1)	*Unmeasured Confounders* All plausible confounders would have reduced the effect (+1)	
Expert Opinion	Very Low			Very Low

Adapted from: Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004, 328 (7454): 1490-1494.
OBS=observational study; RCT=randomized controlled trial

Table 3. Developing and Grading the Clinical Guideline Recommendation

Quality of Evidence	Weighing Risks vs. Benefits	GRADE Recommendation	Clinical Guideline Statement
High to very low	Net benefits outweigh harms	Strong	We recommend
High to very low	Tradeoffs for patient are important	Weak	We suggest
High to very low	Uncertain tradeoffs	Further research needed	We cannot make a recommendation at this time

Adapted from: Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004, 328 (7454): 1490-1494

or project implementation, to wide confidence intervals, to variable results across studies, indirect evidence or suspected publication bias. The quality rating may be upgraded if the effect size is very large, a dose-response gradient is shown, or if all plausible, unreported biases or unmeasured confounders would strengthen the reported treatment effect even further (Table 2). When expert opinion is included, the evidence base is assigned a grade of *very low* and may not be changed.

If the evidence grade is high, it is unlikely that further research will change our confidence in the estimate of effect. With moderate grade evidence, further research is likely to modify the confidence in the effect estimate and may change the estimate. With low grade evidence, further research is very likely to change the estimate, and with very low evidence grades, an estimate of the effect is very uncertain.

A clinical recommendation is then developed by consensus of the Clinical Guidelines authors, based on the best available evidence. The risks and benefits to the patient are weighed in light of the available evidence. Conditional language is used for weak recommendations (Table 3). The summary of clinical guidelines for glucose control in neonates receiving parenteral nutrition is in Table 4.

Question 1

How should blood glucose concentration be determined in neonates? (Tables 5, 6). We suggest that blood glucose screening be conducted by laboratory serum glucose or glucose electrode measurements rather than point of care reagent test strips when possible (weak).

Rationale. Blood glucose measurements taken with point of care reagent strips may be susceptible to error due to

Table 4. Nutrition Support Clinical Guideline Recommendations for Glucose Control in Neonates receiving Parenteral Nutrition

Question 1: How should blood glucose concentration be determined in neonates?	
We suggest that blood glucose screening be conducted by laboratory serum glucose or glucose electrode measurements rather than point of care reagent test strips.	Weak
Question 2: What blood glucose concentration is associated with reduced clinical complications in neonates receiving PN	
We suggest keeping the blood glucose concentration < 150 mg dL	Weak
We cannot make a recommendation to determine whether serum glucose should be maintained > 40 mg/dL	Recommend Further Research
We recommend treating symptomatic hypoglycemia.	Strong
Question 3: What strategies may be used to maintain optimal blood glucose concentration in neonates receiving PN?	
We suggest that excess energy and dextrose delivery be avoided.	Weak
We suggest that fat emulsion be added to PN infusion.	Weak
We recommend against the use of early insulin therapy to prevent hyperglycemia.	Strong
We cannot make a recommendation to evaluate the impact of treating hyper- or hypoglycemia on clinical outcomes.	Recommend Further Research

possible contamination of the blood sample with alcohol which has been shown to increase the blood glucose reading,[18] while an elevated hematocrit may falsely lower the result.[19] Additionally glucose measurements obtained using reagent test strips measure glucose concentrations of whole blood and thus have been found to be as much as 15% lower when compared with laboratory plasma glucose values.[19-20] Plasma glucose measurements have a lower standard deviation between repeated values and are considered the gold standard for monitoring of hypoglycemia.[19] When it is not possible to utilize plasma glucose measurement, the clinician should be aware of these potential sources of error associated with point of care reagent test strips.

Question 2

What blood glucose concentration is associated with reduced clinical complications in neonates receiving PN? (*Tables* 7, 8). We suggest keeping the serum glucose concentration < 150 mg/dL (weak). We cannot make a recommendation to determine whether serum glucose should be maintained > 40 mg/dL (recommend further research). We recommend treating symptomatic hypoglycemia (strong).

Rationale. Hyperglycemia may occur in the neonate receiving PN due to excessive glucose infusion rates, stress, or treatment with certain medications including steroids and methylxanthines.[21] Less effective insulin response to elevated blood glucose levels, probable partial insulin resistance, and a lack of negative feedback on hepatic glucose production during PN dextrose infusion all make the preterm infant particularly susceptible.[21-25]

Historically, hyperglycemia has been defined as whole blood glucose concentration >125 mg/dL or serum glucose concentration > 150 mg/dL.[21,26] Under this definition, the incidence of hyperglycemia in VLBW infants during the first week of life ranges from 40-80%.[7,27] Multiple studies in neonates (particularly those that are low birth weight [LBW] and/or premature) have indicated that persistently elevated serum glucose concentrations of >150 mg/dL are correlated with adverse clinical outcomes and/or increased mortality.[7-9,11,28] Other research identifies a link between increased morbidity and mortality and a serum glucose level >180 mg/dL.[10] Research in this area draws correlations between hyperglycemia and morbidity and mortality, however clinical trials demonstrating causality are lacking.

There is great variability in the definition of neonatal hypoglycemia,[29-36] and a lack of research focusing on hypoglycemia in the neonate receiving PN. Hypoglycemia has been defined as a serum glucose < 40 mg/dL[29], but no firm consensus on this level can be drawn based upon the current literature. As discussed in a review of current research on subsequent neurodevelopmental outcomes following episodes of hypoglycemia in the first week of life, there is a need for a well-designed, prospective study in this area in order to draw accurate conclusions and firmly establish a clinically-relevant definition for neonatal hypoglycemia.[37]

Populations of neonates with increased risk of hypoglycemia include premature, VLBW, ELBW, small for gestational age (SGA) (<10th percentile for age),[38,39] large

Table 5. Evidence Table Question 1: How should blood glucose concentration be determined in neonates?

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Hussain, 2000 [19]	OBS	Infants admitted to NICU over 1 y (N=180)	Compare capillary and venous glucose by test strip to laboratory-measured plasma glucose values	**Mean difference** Between capillary test strips and plasma glucose, -0.058 mmol/L (SD= 1.39) Between venous test strip and plasma glucose, 0.138 mmol/L (SD= 0.96)	Confirms inaccuracy of whole blood glucose test strips compared to plasma glucose values
Reynolds, 1993 [20]	OBS	Infants admitted to NICU over 80 d (N=82)	Compare reagent test strips to laboratory-measured values	Reagent test strips have 82-83% sensitivity, 69-70% specificity for detection of hypoglycemia	

CI = confidence interval, d = days, NICU = neonatal intensive care unit, OBS= observational study, Ref # = reference number, SD = standard deviation, y = years

Table 6. GRADE Table Question 1: How should blood glucose concentration be determined in neonates?

Comparison	Outcome	Quantity, Type Evidence	Findings	Evidence GRADE for Outcome	Overall Recommendation GRADE, Rationale
Test strip vs. measured plasma glucose	SD or CI	2 OBS	Test strip greater error	Low	Low

CI=confidence interval, OBS=observational study, SD=standard deviation

Table 7. Evidence Table for Question 2: What blood glucose concentration is associated with reduced clinical complications in neonates receiving PN?

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Hyperglycemia Studies					
Heimann, 2007 [11]	OBS Large sample size Retrospective record review	Premature VLBW infants 27.4 (24-35) weeks GA with persistently elevated plasma glucose (N=252)	Evaluate mortality related to moderate hyperglycemia defined as 1-3 glucose measures > 150 mg/dL (n=125), severe hyperglycemia defined as ≥ 4 glucose measures > 150 mg/dL (n=45) relative to normoglycemic with no serum glucose measure > 150 mg/dL (n=82)	**Mortality:** Normoglycemia,13.4% Moderate hyperglycemia, 7.2% Severe hyperglycemia, 22.2% Nonsurvivors had lower (< 27 weeks) GA than survivors, $P<0.001$ Sepsis primary cause of death **Hyperglycemia vs. mortality:** Blood glucose levels and frequency hyperglycemia higher in nonsurvivors than survivors (both $P<0.001$) Incidence of hyperglycemia not related to ROP, sepsis or IVH	Hyperglycemia associated with mortality
Aladeen, 2006[28]	OBS Small sample Retrospective record review	Premature VLBW infants mean 26 week (23-34) GA with bacteremia, on ventilator, PN (N=37)	Evaluate mortality, LOS in hyperglycemic as maximal serum glucose > 120 mg/dL vs. normoglycemic as maximal serum glucose ≤ 120 mg/dL Nonsurvivors (n=6) Survivors (n=31) Hyperglycemic survivors (n=20) Normoglycemic survivors (n=11)	**Maximum serum glucose**: Nonsurvivors 241± 46 Survivors 141± 47 mg/dL, ($P<0.001$) Maximum serum glucose related to PN duration (r =0.45, P =0.005), ventilator d (r = 0.45, P =0.006), LOS (r =0.36, P =0.03). **LOS in survivors**: Hyperglycemic 110 d Normoglycemic 62 d, (P =0.006)	Hyperglycemia associated with prolonged LOS and ventilator dependence
Blanco, 2006[8]	OBS Retrospective record review	ELBW infants in first 2 wks life (N=169)	Evaluate risk of BPD, IVH, ROP associated with hyperglycemia as plasma glucose > 150 mg/dL (n=149) vs. normoglycemia as plasma glucose ≤ 150 mg/dL (n=20)	**Prevalence hyperglycemia**, 88%. **Hyperglycemia risk**: Odds of hyperglycemia lower with GA ≥ 26 wk (OR 0.11, 95% CI 0.01-0.89) relative to more premature infants **Hyperglycemia vs. ROP risk**: Odds of ROP, adjusted for GA, BW and postnatal steroid exposure increased in hyperglycemia vs. normoglycemia (OR 4.6, 95% CI 1.12-18.9)	

(continued)

Table 7. (continued)

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Hays 2006[9]	OBS Small sample Retrospective record review	ELBW infants 25.4± 1.9 week GA in 1st wk life (N=82)	Evaluate incidence hyperglycemia as blood glucose 150-250 mg/dL and severe hyperglycemia as mean blood glucose ≥ 250 mg/dL and associated mortality, IVH	**On DOL 2-7,Incidence hyperglycemia** 57% **Incidence severe hyperglycemia** 32% **Hyperglycemia predicts** early death or IVH with 91% sensitivity, 25% specificity **With FiO2>40%, risk of death or IVH**: Normoglycemia, 33% Hyperglycemia, 57%, *P*=0.052. **LOS**: Normoglycemia, 119 d Hyperglycemia, 182 d, *P*<0.05 **With Clinical Risk for Babies score > 8, risk of death or IVH**: Normoglycemia, 20% Hyperglycemia, 43%, *P*<0.05	Hyperglycemia predicts death, LOS
Kao, 2006[10]	OBS Large sample Retrospective analysis of a prospective cohort study	ELBW infants 26.2±1.9 weeks GA in 1st wk life (N=201)	Evaluate prevalence of normoglycemia as serum glucose < 120 mg/dL, mild hyperglycemia as serum glucose 120-179 mg/dL, severe hyperglycemia as serum glucose ≥180 mg/dL vs. mortality and infection	**Prevalence hyperglycemia**: Normoglycemia 65%, Mild hyperglycemia 28%, Severe hyperglycemia 7% **Mild-moderate hyperglycemia vs. death or infection**: Mild-moderate hyperglycemia not significantly associated with death or infection, adjusted for age, *P*=0.09 **Hyperglycemia vs. mortality or infection**: Relative to normoglycemia, severe hyperglycemia in DOL 1-3 increased risk of mortality or infection, (adjusted OR 5.07, 95% CI 1.06-24.3, *P*=0.04) **Hyperglycemia vs. mortality**: Relative to normoglycemia, severe hyperglycemia in DOL 1-3and 1st 7 DOL (adjusted for age) associated with increased risk for mortality (OR 15.7, 95% CI 3.74-65.9, *P*<0.001 and OR 30.4, 95% CI 3.37-274, *P*=0.002 respectively)	

(continued)

Table 7. (continued)

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Lilien, 1979[41]	OBS Small sample No power analysis	Premature VLBW and ELBW infants (N=30)	Evaluate incidence hyperglycemia (as blood glucose > 145 mg/dL) and incidence of IVH and mortality in stressed (n=18) and control (n=12) infants with constant dextrose infusion	**Incidence Hyperglycemia**: Stressed 72.2% Control 8.3% **Outcomes vs. Stress**: **Mortality**: Stressed 83.3% Control 16.7%, $P<0.001$ **IVH**: Stressed 55.6% Control 8.3%, $P<0.05$ **Hyperglycemia vs. Outcomes**: **Mortality**: Hyperglycemic Stressed 84.6% Hyperglycemic Control 0% Normoglycemic Stressed 80% Normoglycemic Control 9% **IVH**: Hyperglycemic Stressed 69.2% Hyperglycemic Control 0% Euglycemic Stressed 20% Euglycemic Control 9%	Stress associated with greater mortality and IVH, but not significantly increased with hyperglycemia
Zarif, 1976[7]	OBS Small sample	Premature VLBW infants (N=75)	Evaluate risk of mortality due to hyperglycemia. Normoglycemia as blood glucose < 125 mg/dL (n=43) Hyperglycemia as blood glucose > 125 mg/dL (n=32)	**Mortality**: Hyperglycemia 59%, Normoglycemia 12%, $X^2 = 19.1$ ($P<0.001$)	
Hypoglycemia Studies					
Burns, 2009[4]	OBS Case control	Term neonates, n=69 Neonates with symptomatic hypoglycemia, n=35 Term neonate controls, n=229	Evaluate neurodevelopmental outcomes at age 18 months and MRI abnormalities at <6 weeks in term neonates with symptomatic hypoglycemia (<1 week of age)	**MRI findings**: WM abnormalities in 94% (43% of these severe) BGT lesion in 40% Cortical abnormalities in 51% WM hemorrhage in 30% PLIC abnormality in 11% **Neurodevelopmental impairment**: None, 8/34 Mild, 15/34 Moderate,8/34 Severe, 3/34	Symptomatic hypoglycemia associated with early brain abnormalities and developmental impairment at 18 mo
Filan, 2006[5]	OBS Case series No control No standard neuro-developmental measures Small sample	Term neonates with symptomatic hypoglycemia (N=4)	Evaluate brain abnormalities by MRI DOL 4-7, 11-50 after hypoglycemia and neurodevelopmental outcomes at 9-12 mo	**MRI Findings**: Abnormalities observed in all **Neurodevelopment impairment**: Microcephaly, gross motor delay, visual impairment in 25%	Symptomatic hypoglycemia associated with abnormal MRI and abnormal neurodevelopment in 25%

(*continued*)

Table 7. (continued)

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Sexson, 1984[29]	OBS Inaccurate glucose test measure No clinical outcomes	All infants born during 4 mo at single institution (N=232) Screened for hypoglycemia if preterm, LGA, SGA, erythroblastosis, CNS abnormality, respiratory distress, temperature instability, asphyxia, meconium staining, polycythemia or perinatal stress (n=168)	Evaluate incidence of hypoglycemia as blood glucose < 40 mg/dL by test strip	**Incidence Hypoglycemia**: Overall, 20.6% At risk infants, 28.6% Mean age at hypoglycemia 3.4 h (range 0.5-12 h) Mean laboratory blood glucose after hypoglycemia by test strip screen 27.6 (range 0-38) mg/dL.	

BGT= basal ganglia or thalamic; BPD= bronchopulmonary dysplasia; BW = birth weight; CI=95% confidence interval; CNS= central nervous system; d = days; DOL= day of life; ELBW= extremely low birth weight (<1000 g); GA = gestational age; GIR= glucose infusion rate; IVH= intraventricular hemorrhage; LGA= large for gestational age; LOS= length of hospital stay; mo = months; MRI=magnetic resonance imaging; OBS = observational study; OR=odds ratio; PLIC= posterior limb of the internal capsule; PN=parenteral nutrition; ROP=retinopathy of prematurity; SGA= small for gestational age; VLBW= very low birth weight (<1500 g); WM= white matter; wk = weeks

Table 8. GRADE Table Question 2: What blood glucose concentration is associated with reduced clinical complications in neonates receiving PN?

Comparison	Outcome	Quantity, Type Evidence	Findings	Starting GRADE	Final GRADE for Outcome	Overall GRADE of Evidence for Recommendation
Hyperglycemia as blood glucose > 150 mg/dL	LOS	1 OBS	Increased	Low	Very low	Low
	Ventilator days	1 OBS	Increased	Low	Very low	
	ROP	1 OBS	Increased	Low	Low	
	Mortality	4 OBS	Increased	Moderate to very low	Low	
Hypoglycemia as blood glucose < 40 mg/dL	Incidence hypoglycemia	1 OBS	Increased	Very low	Very low	Very low
Symptomatic hypoglycemia should be treated	White matter abnormalities on MRI	2 OBS	Increased	Low	Low to very low	Very Low
	Neurodevelopmental abnormalities age 9-12 mo	2 OBS	Increased	Low	Low to very low	

LOS=length of stay; MRI=magnetic resonance imaging; OBS=observational study; ROP=retinopathy of prematurity

for gestational age (LGA) (>90th percentile for age) and severely stressed neonates.[34] Infectious physiology and hyperinsulinemia can also contribute to hypoglycemia in these populations.[34] Prevention of hypoglycemia in this population may therefore require higher thresholds of dextrose provision.[34]

Neonates receiving PN are at a relatively low risk of developing hypoglycemia due to PN dextrose infusion, however receipt of insufficient PN energy provision,[36] loss of central venous access,[40] and the use of cyclic PN may all render the neonate receiving PN susceptible to hypoglycemia. We recommend further research to fill the gaps in evidence regarding hypoglycemia in neonates receiving PN.

Neonates who demonstrate signs or symptoms of hypoglycemia including cyanotic spells, apnea, somnolence, respiratory distress or convulsions[36] should undergo clinical interventions for normalization of serum glucose concentration.[34] Recurrent or symptomatic hypoglycemia may result in neurodevelopmental impairment,[1,4] with the most common and severe sequelae of hypoglycemia including intractable epilepsy, cerebral palsy, mental motor retardation and visual disturbance.[3] Because of the severity of clinical outcomes associated with hypoglycemia in neonates, we recommend treatment of symptomatic hypoglycemia.

At this time high level data are not sufficient to provide specific approaches for the treatment of hyper- and hypoglycemia. Perhaps once the definitions of these conditions are more clearly established, randomized controlled trials can be conducted to determine the safest approaches for management.

Question 3

What strategies may be used to maintain optimal blood glucose concentration in neonates receiving PN? (Tables 9, 10). We suggest that excess energy and dextrose delivery be avoided (weak) and fat emulsion be added to the PN infusion (weak). We recommend against the use of early insulin therapy to prevent hyperglycemia (strong). We cannot make a recommendation to evaluate the impact of treating hyper- or hypoglycemia on clinical outcomes (recommend further research).

Rationale. In order to prevent hypoglycemia, high glucose infusion rates (GIR) are often provided to neonates receiving PN. This, in turn, may lead to hyperglycemia. VLBW infants are, in fact, able to maintain euglycemia at a lower GIR when dextrose is administered in the presence of intravenous fat emulsion, since glycerol is the predominant gluconeogenic substrate.[42-44] In the event

Table 9. Evidence Table for Question 3: What strategies to control blood glucose concentrations are associated with better outcomes in neonates receiving PN?

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Drenckpohl, 2008[53]	RCT Randomized Not blinded	AGA neonates (750-1500 g) receiving PN (N=100) Intervention: Both groups with PN AA 3 g/kg/d, increased per protocol to 3.5 g/kg/d; Dextrose concentration at 10% solution increased as tolerated to 12.5% solution Experimental group (n=48): Infusion of earlier, higher dose of fat emulsion (2 g/kg/day increasing by 0.5 g/kg/day until 3 g/kg/day) Control group (n=52): Intravenous fat emulsion (0.5 g/kg/day, increasing by 0.5 g/kg/day until 3 g/kg/day)	Assess tolerance of higher iv fat emulsion dose	**Days to reach goal intake of 90 kcal/kg/d**: Experimental, 7.38±3.38 Control, 9.44±3.58, (*P*=0.004) **Hypertriglyceridemia**: Experimental, 15% Control, 4%, (*P*=0.06) **Use of insulin**: Experimental, 0% Control, 10% (*P*=0.028) **Wt loss in wk 1**: Experimental, 8% Control, 10%, (*P*=0.034) **Wt ≥ 10%tile at discharge**: Experimental, 17% Control, 4.2%, (*P*=0.007) **Incidence NEC**: Experimental, 0% Control, 14%, (*P*=0.008) **Incidence ROP**: Experimental, 6% Control, 23%, (*P*=0.019)	Improved growth with fewer complications with higher fat emulsion dose
Ibrahim, 2004[54]	RCT Small sample Not blinded	Ventilator-dependent, VLBW infants receiving PN (N=32) Intervention: Early PN group received AA 3.5 g/kg/d with fat emulsion 3 g/kg/d starting 1 h after birth. Late PN group received dextrose only x48hr then AA 2 g/kg/d with fat emulsion 0.5 g/kg/d, with each being increased by 0.5 g/kg/d to max of 3.5 and 3 g/kg/d respectively. Outcomes Measured: Nitrogen retention, energy intake, mean fluid intake, weight gain, laboratory values	Evaluate nutritional and clinical outcomes associated with early vs. late PN	No hyperglycemia in either group. **Nitrogen retention**: Early PN 384.5± 20.2 mg/kg/day Late PN 203.4 ± 20.9 mg/kg/day, (*P*<0.001) **Energy intake**: Early vs. late PN, 78.2 +/-0.42 vs. 59.8 +/- 0.43 kcal/kg/day (*P*<0.001) No differences in BPD, IVH, sepsis, PDA, ROP, or mortality between groups	Nutrient intake better with early than late PN
Sunehag, 2003[42]	OBS Prospective Historical controls Small sample	Premature (GA≤ 29 wk), AGA infants ≥ 750 g (N=14) receiving PN Intervention: On DOL5 GIR decreased to 3 mg/kg/min and either fat emulsion or AA discontinued	Use stable isotopes to measure as outcome of half-normal GIR plus withdrawal of fat emulsion or AA	Significant decrease in gluconeogenesis with withdrawal of fat emulsion (*P*= 0.03) No significant effect on gluconeogenesis of withdrawal of AA	

(continued)

Table 9. (continued)

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Sunehag, 1999[43]	OBS Small sample	Premature (mean GA 27 wk) VLBW infants receiving PN (N=20) PN Intervention: GIR 3 mg/kg/min (half normal turnover rate), fat emulsion 1.6 mg/kg/min, AA 2.2 mg/kg/min	Use stable isotopes to measure as outcome of half-normal GIR	Normoglycemia maintained by gluconeogenesis, using glycerol as principal substrate	
Murdock, 1995[44]	RCT Small sample No power analysis Not blinded	Neonates <2000 g at birth receiving PN (N=29) Intervention: Randomized to one of three PN formulations over 2 d; Glucose 7-10 g/kg/d (n=11) Glucose 7-10 g/kg/d + AA 1-1.4 g/kg/d (n=10) Glucose 7-10 g/kg/d + AA 1-1.4 g/kg/d + fat emulsion 1 g/kg/d (n=8)	Evaluate incidence of hypoglycemia as serum glucose < 46 mg/dL with 3 PN formulations	**Incidence hypoglycemia**: Glucose (n=6/11) Glucose + AA (n=9/10) Glucose + AA + fat (n=2/8)	
Collier, 1994[45]	OBS Small sample	PN-dependent infants age 1-6 mo (N=10) Interventions: Cycled PN (schedule of 1-2 h off PN initially, followed by advancement of 1-2 h additionally daily as tolerated up to maximum 6 h off PN for patients with no enteral feedings)	Evaluate incidence of hypoglycemia as blood glucose (<40 mg/dL) at 30-60 min after PN off, then again halfway through the period without PN in response to cycled PN	No clinical hypoglycemia observed	Time off PN limited to 6 hours
Dweck, 1974[27]	OBS Small sample No acuity measure	ELBW infants with glucose measures in DOL 1-10 (N=50) Normoglycemia as serum glucose <125 mg/dL (n=7) Moderate hyperglycemia as serum glucose 126-300 mg/dL (n=7) Severe hyperglycemia as serum glucose >300 mg/dL (n=36)	Evaluate incidence of hyperglycemia in relation to GIR	**Severe hyperglycemia**: More common with GIR > 0.4 g/kg/hr than with ≤ 0.4 g/kg/hr (X^2= 8.25, P<0.005). **Incidence severe hyperglycemia**: With GIR ≤0.4 g/kg/hr PN alone, 47%PN + oral glucose, 13% (P<0.005) With GIR > 0.4 g/kg/hr, PN alone, 65% PN + oral glucose, 41%(P<0.005)	GIR predicts hyperglycemia

(continued)

Table 9. (continued)

Author, Year (ref #)	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Insulin Infusion Studies					
Beardsall, 2008[50]	RCT Large sample Not blinded	VLBW infants recruited over 2 y, followed through expected date of delivery (N=389)	Evaluate outcomes (mortality, incidence of hypoglycemia [glucose <2.6 mmol/L]) associated with early insulin therapy to prevent hyperglycemia (glucose >10 mmol/L). In addition to PN, randomized to: Early insulin infusion 0.05 units/kg/hr + 20% dextrose to maintain euglycemia [glucose 4-8 mmol/L] (n=194) vs. Control with standard of care glucose management (n=192)	Trial discontinued early due to futility and concern for safety of pts in early insulin group. **Mortality**: Early insulin 14.4% Control 9.4% ITT analysis greater mortality in early insulin group (*P*=0.04) Trend of increased IVH, parenchymal lesions, death in treatment group. **Hyperglycemia incidence**: Early insulin 21% Control 33%, *P*=0.008 **Hypoglycemia incidence**: Insulin infusion, 29% Control, 17%, *P*=0.005 OR 2.21, 95% CI 1.34-3.65 **Mean glucose**: Insulin, 112±25.2 mg/dL Control, 121±39.6 mg/dL, (P= 0.007)	
Meetze, 1998[49]	RCT Small sample	ELBW infants on DOL#2 who required PN (N=56)	Evaluate energy intake, hypoglycemia, IGF-1, IGF-2 Interventions: GIR increased gradually to max of 12 mg/kg/min. Infants with hyperglycemia randomized to: Insulin infusion (n=12) Reduced GIR (n=11) Control, normoglycemic infants (n = 33)	**Days with intake >60 kcal/kg/d**: Insulin 5.5 ± 0.6 d Reduced GIR 8.6 ± 1.3 d Control 4.1 ± 0.2, (*P*<0.01) No incidence of hypoglycemia with insulin No correlation between hyperglycemia and IGF-I or IGF-II	
Collins, 1991[48]	RCT Small sample	ELBW infants age 4-14 d with serum glucose >180 mg/dL, glucosuria, and receiving PN (N=24)	Compare biochemical outcomes and weight gain with randomization to Continuous insulin infusion vs. Control, insulin coverage	**GIR**: Insulin infusion, 20.1 ± 2.5 mg/kg/min Control, 13.2± 3.2 mg/kg/min, (*P*<0.01) Fewer than 1% glucose levels <40 mg/dL in insulin infusion group **Weight gain**: Greater mean daily weight gain in insulin infusion group (*P* <0.01) with no significant difference in length or head circumference	Note that insulin group received extremely high GIR.

AA= amino acid; AGA= appropriate weight for gestational age; BPD = bronchopulmonary disease; d = days; DOL = day of life; ELBW = extremely low birth weight; GA=gestational age; GIR = glucose infusion rate; ITT = intention-to-treat; IVH=intraventricular hemorrhage; LOS=length of hospital stay; mo = months; NEC = necrotizing enterocolitis; OBS = observational study; OR = odds ration; PDA = patent ductus arteriosus; PN= parenteral nutrition; RCT = randomized controlled trial; ROP = retinopathy of prematurity; SR=systematic review; VLBW= very low birth weight; wt = weight; y = years

Table 10. GRADE Table for Question 3

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
Insulin infusion	Mortality	1 RCT	Increase	High	High
	Weight Gain	2 RCT	Increase	High to Moderate	
Reduced GIR	Energy Intake	1 RCT	Increase	Moderate	Moderate
Fat emulsion	Energy Intake, Nitrogen Retention	1 RCT	Increase, Increase	Moderate	Moderate
	NEC, ROP	1 RCT	Reduce, Reduce	Moderate	

GIR=glucose infusion rate; NEC = necrotizing enterocolitis; RCT= randomized controlled trial,; ROP= retinopathy of prematurity

that hyperglycemia does occur in the setting of high dose intravenous fat emulsion provision, lowering the fat emulsion dose should be considered due to its role in gluconeogenesis. In patients receiving cycled PN, intravenous dextrose and PN formulations should be tapered off over 1-2 hours to prevent reactive hypoglycemia.[45,46]

There has been substantial research regarding the use of early, continuous insulin infusion to prevent hyperglycemia in the neonate. While a number of small studies suggest a benefit [47-49], other larger studies have raised significant concerns regarding this practice. Specifically, a large RCT by Beardsall et al. was terminated early due to increased incidence of hypoglycemia and mortality in the early continuous insulin infusion group.[50] A recent Cochrane review also determined that there is insufficient evidence to recommend early, continuous insulin infusion.[51] Finally, in a euglycemic insulin clamp model, Poindexter et al. demonstrated a 3-fold increase in plasma lactate levels in ELBW infants treated with continuous insulin infusion, with no net protein anabolic effect observed.[52]

Although routine early, continuous insulin infusion is not recommended, persistent hyperglycemia in the neonate receiving PN may warrant treatment with insulin. Insulin should be used only for those patients in whom other methods of glucose control, such as reduction of glucose infusion rates, elimination of medications predisposing patients to hyperglycemia, and correction of underlying causes of hyperglycemia (i.e., sepsis) have failed.

Acknowledgements

We appreciate the contributions of Pat Worthington, MSN, RN, CNSN, Marty Kochevar, MS, RPh, BCNSP; and Elizabeth Robinson, BA, Research Coordinator in the Department of Surgery at Children's Hospital Boston

A.S.P.E.N. Board of Directors providing final approval: Charles Van Way III, MD (Chair); Mark DeLegge, MD; Carol Ireton-Jones, PhD, RD, LD, CNSD; Tom Jaksic, MD, PhD; Elizabeth M. Lyman, RN, MSN; Ainsley M. Malone, RD, MS; Stephen A. McClave, MD; Jay M. Mirtallo, MS, RPh, BCNSP, FASHP; Lawrence A. Robinson, PharmD; W. Frederick Schwenk MD, CNSP; and Daniel Teitelbaum, MD.

A.S.P.E.N. Clinical Guidelines Editorial Board: Charlene Compher, PhD, RD, FADA, CNSC (Editor in Chief); Joseph Boullata, PharmD, BCNSP; Carol Braunschweig, PhD, RD; Mary Ellen Druyan, PhD, MPH, RD, CNS, FACN; Donald George, MD; Edwin Simpser, MD; and Patricia Worthington, MSN, RN, CNSN

References

1. Duvanel C, Fawer C, Cotting J, Hohlfeld P, Matthieu J. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *J Pediatr* 1999;134(4):492-8.
2. Lucas A, Morley R, Cole T. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988;297(6659):1304-8.
3. Per H, Kumandas S, Coskun A, Gumus H, Oztop D. Neurologic sequelae of neonatal hypoglycemia in Kayseri, Turkey. *J Child Neurol* 2008;23:1406-12.
4. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics* 2008;122(1):65-74.
5. Filan PM, Inder TE, Cameron FJ, Kean MJ, Hunt RW. Neonatal hypoglycemia and occipital cerebral injury. *J Pediatrics* 2006;148(4):552-5.
6. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. *Seminars In Neonatology SN* 2001;6(2):147-55.
7. Zarif M, Pildes R, Vidyasagar D. Insulin and growth-hormone responses in neonatal hyperglycemia. *Diabetes* 1976;25(5):428-33.
8. Blanco C, Baillargeon J, Morrison R, Gong A. Hyperglycemia in extremely low birth weight infants in a predominantly Hispanic population and related morbidities. *J Perinatol* 2006;26:737-41.
9. Hays S, O'Brian Smith E, Sunehag A. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. *Pediatrics* 2006;118:1811-8.
10. Kao L, Morris B, Lally K, Stewart C, Huseby V, Kennedy K. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. *J Perinatol* 2006;26:730-6.

11. Heimann K, Peschgens T, Kwiecien R, Stanzel S, Hoernchen H, Merz U. Are recurrent hyperglycemic episodes and median blood glucose level a prognostic factor for increased morbidity and mortality in premature infants ≤ 1500 g? *J Perinat Med* 2007;35:245-8.
12. A.S.P.E.N. Board of Directors. Guidelines for use of total parenteral nutrition in the hospitalized adult patient. *JPEN J Parenter Enteral Nutr* 1986;10(5):441-445.
13. A.S.P.E.N: Board of Directors. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. *JPEN J Parenter Enteral Nutr* 1993;17(Suppl 4):1SA-52SA.
14. A.S.P.E.N: Board of Directors. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. *JPEN J Parenter Enteral Nutr* 2002;26:1SA-138SA. (Errata 2002;26:114).
15. Jadad AR, Moore RA, et al. Assessing the quality of reports or randomized clinical trials: Is blinding necessary? *Controlled Clin Trials* 1996;17:1-12.
16. Altman DG, Schulz KF, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001;134:663-694.
17. Guyatt GH, Oxman AD, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
18. Grazaitis D, Sexson W. Erroneously high Dextrostix values caused by isopropyl alcohol. *Pediatrics* 1980;66(2):221-3.
19. Hussain K, Sharief N. The inaccuracy of venous and capillary blood glucose measurement using reagent strips in the newborn period and the effect of haematocrit. *Early Hum Dev* 2000;57(2):111-21.
20. Reynolds G, Davies S. A clinical audit of cotside blood glucose measurement in the detection of neonatal hypoglycaemia. *J Paediatr Child Health* 1993;29(4):289-91.
21. Mitanchez D. Glucose regulation in preterm newborn infants. *Horm Res* 2007;68:265-71.
22. Cowett R, Schwartz R. Persistent glucose production during glucose infusion in the neonate. *J Clin Invest* 1983;71:467-75.
23. Sunehag A, Gustafsson J, Ewald U. Very immature infants (< or = 30 wk) respond to glucose infusion with incomplete suppression of glucose production. *Pediatr Res* 1994;36:550-5.
24. Farrag H, Nawrath L, Healey J, et al. Persistent glucose production and greater peripheral sensitivity to insulin in the neonate vs. the adult. *Am J Physiol* 1997;272:E86-E93.
25. Mericq V. Prematurity and insulin sensitivity. *Horm Res* 2006;65 (suppl 3) 131-6.
26. Yeung M. Glucose intolerance and insulin resistance in extremely premature newborns, and implications for nutritional management. *Acta Paediatr* 2006;95:1540 – 7.
27. Dweck H, Cassady G. Glucose intolerance in infants of very low birth weight. I. Incidence of hyperglycemia in infants of birth weights 1,100 grams or less. *Pediatrics* 1974;53(2):189-95.
28. Alaedeen D. Total parenteral nutrition associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. *J Pediatr Surg* 2006;41:239-44.
29. Sexson W. Incidence of neonatal hypoglycemia: a matter of definition. *J Pediatr* 1984;105(1):149-50.
30. Srinivasan G, Pildes R, Cattamanchi G, Voora S, Lilien L. Plasma glucose values in normal neonates: a new look. *J Pediatr* 1986; 109(1):114-7.
31. Heck L, Erenberg A. Serum glucose levels in term neonates during the first 48 hours of life. *J Pediatr* 1987;110(1):119-22.
32. Koh T, Eyre J. Aynsley-Green A. Neonatal hypoglycaemia--the controversy regarding definition. *Arch Dis Child* 1988;63(11):1386-8.
33. Tanzer F, Yazar N, H Y, Icagasioglu D. Blood glucose levels and hypoglycaemia in full term neonates during the first 48 hours of life. *J Trop Pediatr* 1997;43(1):58-60.
34. Cornblath M, Hawdon J, Williams A, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000;105(5):1141-5.
35. Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood glucose levels in a population of healthy, breast fed, term infants of appropriate size for gestational age. *Arch Dis Child Fetal Neonatal Ed* 2000;83(2):F117-9.
36. Sperling M, Mennon R. Differential diagnosis and management of neonatal hypoglycemia. *Pediatr Clin North Am* 2004;51:703 – 23.
37. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. *Pediatrics* 2006;117(6):2231-43.
38. Holtrop P. The frequency of hypoglycemia in full-term large and small for gestational age newborns. *Am J Perinatol* 1993;10(2):150-4.
39. Doctor B, O'Riordan M, Kirchner H, Shah D, Hack M. Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. *Am J Obstet Gynecol* 2001;185(3): 652-9.
40. Fook-Choe R, Boo N. An unusual case of refractory hypoglycemia in a neonate receiving parenteral nutrition. *Acta Paediatr* 2000;89:497-8.
41. Lilien L, Rosenfield R, Baccaro M, Pildes R. Hyperglycemia in stressed small premature neonates. *J Pediatr* 1979;94(3):454-9.
42. Sunehag A. The role of parenteral lipids in supporting gluconeogenesis in the very premature infants. *Pediatr Res* 2003;54(4):480-6.
43. Sunehag A, Haymond M, Schanler R, Reeds P, Bier D. Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. *Diabetes* 1999;48:791-800.
44. Murdock N, Crighton A, Nelson L, Forsyth J. Low birthweight infants and total parenteral nutrition immediately after birth. II. Randomized study of biochemical tolerance to intravenous glucose, amino acids and lipid. *Arch Dis Child* 1995;73: F8 – F12.
45. Collier S, Crouch J, Hendricks K, Caballero B. Use of cyclic parenteral nutrition in infants less than 6 months of age. *Nutr Clin Pract* 1994;9(2):65-8.
46. Bendorf K, Friesen C, Roberts C. Glucose response to discontinuation of parenteral nutrition in patients less than 3 years of age. *JPEN J Parenter Enteral Nutr* 1996;20(2):120-2.
47. Beardsall K, Ogilvy-Stuart A, Frystyk J, et al. Early elective insulin therapy can reduce hyperglycemia and increase insulin-like growth factor-I levels in very low birth weight infants. *J Pediatr* 2007;151(6):611-7, 7.e1. Epub 2007 Aug 10.
48. Collins J, Hoppe M, Brown K, Edidin D, Padbury J, Ogata E. A controlled trial of insulin infusion and parenteral nutrition in extremely low birth weight infants with glucose intolerance. *J Pediatr* 1991;118(6):921-7.
49. Meetze W, Bowsher R, Compton J, Moorehead H. Hyperglycemia in extremely-low-birth-weight infants. *Biology of the Neonate* 1998;74:214-21.
50. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart A, et al. Early insulin therapy in very-low-birth-weight infants. *N Eng J Med* 2008;359(18.):1873-84.
51. Bottino M, Cowett R, Sinclair J. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. In: The Cochrane Collaboration: John Wiley & Sons, Ltd; 2009.
52. Poindexter B, Karn C, Denne S. Exogenous insulin reduces proteolysis and protein synthesis in extremely low birth weight infants. *J Pediatr* 1998;132(6):948-53.
53. Drenckpohl D, McConnell C, Gaffney S, Niehaus M, Macwan K. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. *Pediatrics* 2008; 122(4):743-51.
54. Ibrahim H, Jeroudi M, Baier R, Ramasubbareddy D, Krouskop R. Aggressive early total parenteral nutrition in low-birth-weight infants. *J Perinatol* 2004;24:482-6.