# Academy of Breastfeeding Medicine
# HYPOGLYCEMIA AND THE BREASTFED NEONATE
# Annotated Bibliography

| Reference | Content | Level of Evidence* |
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| **General Hypoglycemia Review Articles** | | |
| Garg M, Devaskar SU. Glucose metabolism in the late preterm infant. **Clin Perinatol** 2006; 33(4):853-870 | Review of perinatal glucose metabolism, pathophysiology, definitions, possible neurologic sequellae and modes of prevention of hypoglycemia in the preterm and full-term infant. The primary message is that late preterm infants may be more prone to hypoglycemia because of lower glucose levels during transition and immature compensatory mechanisms. | III |
| Dekelbab BH, Sperling MA. Hypoglycemia in newborns and infants. **Adv Pediatr** 2006; 53:5-22 | Review of the various causes and basic pathophysiology of hypoglycemia in newborns and infants, including congenital disorders. | III |
| Deshpande S, Ward Platt M. The investigation and management of neonatal hypoglycemia. **Semin Fetal Neonatal Med** 2005; 10(4):351-361 | Review of diagnosis and treatment of neonatal hypoglycemia. The authors note that the vast majority of instances of neonatal hypoglycemia are due to problems with the normal processes of metabolic adaptation after birth, and strategies to enhance the normal adaptive processes should help prevent such episodes. | III |
| Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia. Pediatr Clin N Am 2004; 51:703-723 | Review of differential diagnosis of neonatal hypoglycemia with concentration on persistent hypoglycemia, especially inborn errors of metabolism and congenital hyperinsulinism. | III |
| Cowett RM, Loughead JL. Neonatal glucose metabolism: differential diagnosis, evaluation, and treatment of hypoglycemia. **Neonatal Network** 2002; 21(4):9-19 | Review of neonatal glucose metabolism, differential diagnosis, evaluation and treatment of hypoglycemia in the newborn. | III |
| Eidelman AI. Hypoglycemia and the breastfed neonate. **Pediatr Clin N Am** 2001; 48(2):377-387 | Review of glucose homeostasis, definition, causes and management of hypoglycemia in the breastfed infant with recommendations for prevention and treatment. | III |
| Noerr B. State of the science: neonatal hypoglycemia. **Advances in Neonatal Care** 2001; 1(1):4-21 | Comprehensive review of all aspects of hypoglycemia in the newborn including fetal and neonatal glucose homeostasis, the pathophysiology of hypoglycemia, neonatal neural protective mechanisms, approaches to the definition of hypoglycemia, symptoms of neonatal hypoglycemia, risk factors for hypoglycemia, and clinical management strategies. There is a simple table on how to calculate neonatal glucose requirements and therapy. | III |
| Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC. Controversies regarding definition of neonatal | A review encompassing a historical perspective, metabolism and extra-uterine adaptation, risk factors for both term and preterm infants, and recommendations regarding “operational thresholds”, values below which some action needs to be | III |

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| hypoglycemia: suggested operational thresholds. **Pediatrics**. 2000; 105(5):1141-5 | taken. "Significant hypoglycemia is not and can never be defined by a single number that can be applied universally to every individual patient. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiological maturity and the influence of pathology." | |
| McGowan JE. Neonatal hypoglycemia. **NeoReviews** July 1999. Available at: www.neoreviews.org | Review of pathophysiology, incidence, diagnosis, clinical presentation, etiology, and clinical consequences of hypoglycemia in the newborn. | III |
| Halamek LP, Benaron DA, Stevenson DK. Neonatal hypoglycemia, Part I: Background and definition. **Clin Pediatrics** 1997; 36:675-680 | Review of historical aspects, glucose homeostasis, methods of measuring glucose concentrations, possible definitions of hypoglycemia and neonatal conditions associated with hypoglycemia. | III |
| Halamek LP, Stevenson DK. Neonatal hypoglycemia, Part II: Pathophysiology and therapy. **Clin Pediatrics** 1997; 37:11-16 | Review of hypoglycemia mechanisms of injury, long-term sequellae with recommendations for screening and treatment. Hypoglycemia is defined as < 30 mg/dL (1.66 mmol/L) in the first 24 hrs of life and < 45 mg/dL (2.5 mmol/L) thereafter. | III |
| Williams, Anthony F. Hypoglycaemia of the Newborn: Review of the Literature. World Health Organization, Geneva, 1997; 56 pages (Download from: www.who.int/chd/pub/imci/bf/hypoglyc/hypoclyc.htm) | A comprehensive review of the literature, as of 1997, of all aspects of neonatal hypoglycemia including historical background, glucose homeostasis and metabolic adaptation at birth, short and long-term effects of hypoglycemia on the infant, definitions of hypoglycemia and screening, prevention and treatment. Evidence-based recommendations for prevention and management are summarized at the beginning. Covers both breastfed and formula-fed infants. | III |
| Cornblath M, Reisner SH. Blood glucose in the neonate and its clinical significance. **NEJM** 1965; 273: 378-80 | Review of the statistical definitions of hypoglycemia and normal pattern of self-limited initial hypoglycemia. | III |
| **Metabolic Adaptation** | | |
| de Rooy L, Hawdon J. Nutritional factors that affect the postnatal metabolic adaptation of full-term small- and large-for-gestational-age infants. Pediatrics 2002; 109(3):e42 http://www.pediatrics.org/cgi/content/full/109/3/e42 (Last accessed 2/14/07) | This was a prospective study of 65 SGA (≤ the 2nd percentile) and 39 LGA (≥ the 98th percentile) full term infants. Anthropometry was performed within the first 48 hours and blood glucose and ketone body concentrations were measured pre-feed for the first 7 postnatal days. There was full support of breastfeeding and close clinical observation. Infants were exclusively breastfed, breastfed with formula milk supplementation, or exclusively formula fed. Within the SGA group, a measure of "thinness" (the mid arm circumference/head circumference ratio) was significantly correlated with the number of episodes of blood glucose < 2.0 mmol/L. In these SGA infants the ketone body concentration was significantly higher for those SGA infants who were exclusively breastfed. For LGA infants, low blood glucose levels were offset by ketone body concentrations equivalent to those observed in infants who were AGA. The conclusions were that the neonatal ability to generate ketone bodies when blood glucose values | II-2 |

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| | were low depended more on successful breastfeeding than on the size for gestational age or neonatal nutritional status. Routine blood glucose monitoring of LGA infants with no additional risk factors is not necessary and that routine formula supplementation for LGA and SGA infants should not be recommended. | |
| de L Costello AM, Pal DK, Manandhar DS, Rajbhandari S, Land JM, Patel N,. Neonatal hypoglycaemia in Nepal 2.Availability of alternative fuels. **Arch Dis Child Fetal Neonatal Ed** 2000; 82:F52-F58 | This was a cross sectional study done of 578 neonates from 0-48 hours of life in the main maternity hospital in Kathmandu, Nepal. Blood glucose, hydroxybutyrate, lactate, pyruvate, free fatty acids and glycerol were measured. Risk factors for impaired metabolic adaptation were common, especially in low birthweight, feeding delays, and cold stress. Blood glucose and ketones rose with age. Alternative fuel concentrations, except for free fatty acids, were significantly reduced in infants with moderate hypoglycemia during the first 48 hours after birth. Hypoglycemic infants were not hyperinsulinemic. Regression analysis showed risk factors for impaired counter regulation included male sex, LGA infants, hypothermia and poorer infant thyroid function. Interestingly SGA infants and those whose mothers had received no prenatal care had improved counter regulation. They concluded that alternative fuels were important in the metabolic assessment of neonates and that they might provide effective cerebral metabolism, even during moderate hypoglycemia. | II-2 |
| Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term neonates in the first postnatal week. **Arch Dis Child** 1992; 67: 357-65 | This was a cross-sectional study of 156 term, and 62 preterm infants to establish the normal ranges and interrelationships of blood glucose and intermediary metabolites in the first postnatal week and to compare these with those of 52 older children. Blood glucose concentrations varied more for the preterm than for the term infants and preterm infants had low ketone body concentrations, even at low blood glucose concentrations. Breastfeeding of term infants and enteral feeding of preterm infants appeared to enhance ketogenic ability. The term infants had lower prefeed blood glucose concentrations than children, but, like children, appear to be capable of producing ketone bodies. Breastfed infants up to one week of age had significantly lower mean blood glucose concentrations (mean 3.6 mmol/L) than formula fed infants of the same age (mean 4.0 mmol/L). They concluded that neonatal blood glucose concentrations should be considered in the context of availability of other metabolic fuels (lactate, pyruvate, alanine, glycerol, non-esterified fatty acids, ketone bodies), and that preterm infants may have a limited ability to mobilize these alternative fuels. | II-2 |
| Lucas A, Bayes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in 6 day old term infants: differences between breast and cow's milk formula feeding. **Acta Paediatr Scand** 1981; 70: 195-200 | Plasma concentrations of insulin, glucagon and gastric inhibitory peptide along with blood levels of glucose, ketone bodies, pyruvate, lactate and glycerol were measured pre- and post-prandially in 76 healthy 6 day old term infants who had been either breastfed or fed on a modified cows milk formula from birth. Formula fed infants had a greater insulin and gastric inhibitory peptide response to feeding and their basal and post-prandial blood ketones were considerably | II-2 |

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| | lower than in breastfed infants. There was also a significantly greater post-feeding rise in both lactate and pyruvate concentrations observed with formula feeding. | |
| Sweet DG, Hadden D, Halliday HL. The effect of early feeding on the neonatal blood glucose level at 1-hour of age. **Early Hum Dev** 1999; 55(1):63-66 | Seventy-five term infants of non-diabetic pregnancies had their capillary glucose measured at one hour of age using the HemoCue B-Glucose system to see if the timing and method of early feeding would influence the result. Of the 75 term infants, 22 were breastfed, 24 bottle fed, and 29 not fed during the first hour after birth. The mean whole blood glucose results were 2.34 mmol/L, 2.52 mmol/L, and 2.58 mmol/L respectively, which were not significantly different. The breastfed and bottle fed groups were fed at a median of 22 minutes prior to sampling. They concluded that the timing and method of early feeding in the newborn had no significant affect on the blood glucose level measured at one hour of age. Please note that the glucose level of the non-fed infants was the same as, or slightly higher than, those that were fed. | II-3 |
| Aylott M. The neonatal energy triangle. Part 1: metabolic adaptation. **Paediatr Nurs** 2006; 18(6):38-42 | Review article giving an general overview of the neonatal transition period during the first 6-10 hours of life. The triangle consists of hypothermia, hypoglycemia and hypoxia. This article describes the normal metabolic adaptation at birth and the difficulties of recognizing and treating hypoglycemia. | III |
| Hume R, Burchell A, Williams FLR, Koh DKM. Glucose homeostasis in the newborn. **Early Human Development** 2005; 81:95-101 | Review of hormonal and metabolic regulation of glucose metabolism in term and preterm infants. | III |
| Cowett RM, Farrag HM. Selected principles of perinatal-neonatal glucose metabolism. **Sem in Neonatology** 2004; 9:37-47 | Review of the definition of euglycaemia, the measurement of rate of glucose production and utilization of glucose by the neonate and discussion of where further work is needed to understand the control of glucose homeostasis in the newborn. | III |
| Karp TB, Scardino C, Butler LA. Glucose metabolism in the neonate: The short and sweet of it. **Neonatal Network** 1995 Dec; 14(8):17-23 | This article reviews concepts of normal glucose metabolism, starting with a review of normal adult glucose and energy metabolism and then reviewing maternal, fetal, and neonatal concepts. Hypoglycemia is discussed, and two selected states: excessive glucose utilization and insufficient supply are used to illustrate the physiology, pathophysiology, diagnosis, treatment and nursing care. This is an excellent basic review designed for neonatal nurses. | III |
| Cornblath M, Schwartz R. **Disorders of Carbohydrate Metabolism in Infancy.** 3rd ed. Boston, MA: Blackwell Scientific Publications, 1991 | Extensive textbook of carbohydrate metabolism in infancy including a detailed discussion of all aspects of neonatal hypoglycemia. Basic reference for statement that measured plasma and serum glucose concentrations are 10-15% higher than whole blood. | III |
| Edmond J, Auestad N, Robbins RA et al. Ketone body metabolism in the neonate: development and the effect of diet. **Federation Proceedings** 1985; 44: 2359-64 | Review of ketone metabolism in animals and man. | III |
| **Incidence & Definitions of Hypoglycemia** | | |

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| Diwakar KK, Sasidhar MV. Plasma glucose levels in term infants who are appropriate size for gestation and exclusively breast fed. **Arch Dis Child Fetal Neonatal Ed** 2002; 87:F46-F48 | Plasma glucose was serially determined in each of 200 healthy, term, AGA infants at 3, 6, 24, and 72 hours of age. In 112 of the 800 samples (14%) thus analyzed, glucose levels were "low" (< 2.2 mmol/L at and before 24 hours of age, and < 2.5 mmol/L at 72 hours of age). No infant had symptomatic or persistent hypoglycemia requiring intervention. Infants found to have low glucose were clinically reexamined, given an additional breastfeed and plasma glucose reassessed after 30 minutes. All infants were asymptomatic and attained euglycemic levels after an additional feed. Delays in transferring mothers to the postnatal ward resulted in 58 of the 70 infants delivered by cesarean section remaining unfed for their first three hours, with 32 of them being fed only after six hours. Satisfactory glucose levels were maintained even when infants remained unfed up to six hours of age. They concluded that plasma glucose levels are satisfactorily maintained in normal term infants without resort to prelacteal feeds. Mode of delivery, parity of the mother, and interval between feeds did not influence the plasma glucose. They also indicated that biochemical thresholds for hypoglycemia did not seem to be of practical importance in asymptomatic, normal, term, breastfed infants. | II-2 |
| Ishikawa N. Natural progress of blood glucose in full-term low-grade low-birthweight infants. **Pediatrics International** 2002; 44:583-589 | The authors measured blood glucose via bedside reagent strip (confirmed with laboratory plasma glucose as needed) at birth, 0.5, 1, and 4 hrs after birth and before the first bottle feeding of dextrose solution at 6-8 hrs of life in 49 "low-grade" LBW infants (2100-2500g) and 38 normal birth weight infants from 37-40 wks gestation. No infant was breastfed, and all infants were in the observation nursery. Hypoglycemia was defined as a blood glucose < 30 mg/dL. No infant had symptoms of hypoglycemia and only 5 infants had blood glucose levels < 30. All rose spontaneously within 30 minutes. The "low-grade" LBW infants of 38-40 weeks had glucose values the same as their larger counterparts. The 37 wk "low-grade" LBW infants had only slightly lower values at 0.5 and 1 hr after birth. Plasma glucose (laboratory) correlated closely (R=0.924) with bedside blood glucose with the plasma value 15% higher than whole blood, consistent with earlier studies. They concluded that gestational age, rather than weight, was more important when screening for hypoglycemia. | II-2 |
| Adejuyigbe EA, Fasubaa OB, Ajose OA, Onayade AA. Plasma glucose levels in exclusively breastfed newborns in the first 48 hours of life in Ile-Ife, Nigeria. **Nutrition and Health** 2001; 15:121-126 | 91 healthy term newborns had maternal and cord glucose measured within 30 minutes of delivery and the infants had glucose measured again at 24 and 48 hours of life before breastfeeding. All mothers were assisted in positioning and attaching their babies to the breast and infants were fed ad lib on demand thereafter. All mothers were euglycemic, while 7 of the 91 neonates had plasma glucose levels <1.7 mmol/L (30mg/dL) at birth. Only one neonate had persistent hypoglycemia from birth to 12 hours of age and required treatment. All the other | II-2 |

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| | neonates had blood glucose levels above 1.7 mmol/L at 24 and 48 hours of life. Weight loss was appropriate for term infants. They concluded that exclusively breastfed newborns had adequate glucose supply and were not at risk for having hypoglycemia in the first 48 hours of life. The mean cord plasma glucose was 3.548, mean plasma glucose at 24 hours was 3.184 and 3.289 at 48 hours of life. | |
| 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:F117-119 | This was a cross sectional study of 223 healthy, breastfed, term infants of appropriate size for gestational age with blood glucose determined at different times between 1 and 96 hours after delivery. All infants were breastfed on demand. Blood glucose concentrations within the first 24 hours after birth were significantly lower (median 3.0 mmol/L) than those after 24 hours of life (median 3.4 mmol/L). No infants, including those with the two lowest blood glucose concentrations of 1.4 and 1.9 mmol/L, had clinical signs of hypoglycemia. There was no significant differences in blood glucose concentration between boys and girls, between infants of smokers and non smokers, between infants delivered vaginally or by cesarean section, or between infants delivered without analgesia and those delivered with epidural or spinal analgesia. From this study they concluded that the occurrence of low blood glucose concentrations in healthy, exclusively breastfed infants of appropriate size for gestational age was very rare and that screening in those infants was not indicated. | II-2 |
| Pal DK, Manandhar DS, Rajbhandari S, Land JM, Patel N, de L Costello AM. Neonatal hypoglycaemia in Nepal 1. Prevalence and risk factors. **Arch Dis Child Fetal Neonatal Ed** 2000; 82:F46-F51 | A cross sectional study was done of 578 term newborn infants age 0-48 hours on the post natal wards of a government maternity hospital in Kathmandu, Nepal to look for risk factors associated with moderate hypoglycemia which was defined as a blood glucose < 2.0 mmol/L. 41% of the newborn infants had mild (< 2.6 mmol/L) and 11% had moderate hypoglycemia (< 2.0 mmol/l). Significant, independent risk factors for moderate hypoglycemia included post-maturity (OR 2.62), birth weight < 2.5 kilos (OR 2.11), infant hemoglobin >210 g/L (OR 2.77), and elevated maternal thyroid simulating hormone (TSH) (OR 3.08). Feeding delay increased the risk of hypoglycemia at age 12-24 hours (OR 4.09). | II-2 |
| Durand R, Hodges S, LaRock S et al. The effect of skin-to-skin breast-feeding in the immediate recovery period on newborn thermoregulation and blood glucose values. **Neonatal Intensive Care** 1997; March-April: 23-29 | This study explored the effects of skin-to-skin breastfeeding in the immediate recovery period on newborn thermoregulation and blood glucose values. A convenience sample of 25 subjects in each of the experimental or control group was recruited. All subjects were Hispanic. These subjects self-selected into the experimental or control group based on their desire to breastfeed or formula feed. For the purposes of the project the experimental group consisted of newborns who are exclusively breastfed in the skin-to-skin position, who received no additional oral intake and who obtained a score of 5 or > on the LATCH scale. The control group consisted of newborns that were taken to the transition nursery, placed under radiant warmers and received 15 milliliters each of formula and 5% glucose water. Newborns in the skin-to-skin breastfeeding group maintained higher mean | II-2 |

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| | temperature values than the infants in the radiant warmer formula feeding group at the two-hour measurement. Both groups maintained mean glucose levels which were in the normal range. There were no statistically significant differences noted between the two groups in initial glucose but the skin-to-skin breastfeeding group had a statistically significantly lower, although still normal, two-hour glucose measurement. The mean two-hour glucose in the skin-to-skin breastfeeding group was 62.3 and in the formula feeding radiant warmer group 71.8. The authors noted that initial skin-to-skin care and breastfeeding is safe and supportive of long-term breastfeeding as per WHO guidelines. | |
| Cole MD, Peevy K. Hypoglycemia in normal neonates appropriate for gestational age. **J Perinatol** 1994; 14(2):118-120 | Prospective study of cord glucose and blood glucose within the first 2 hours of age of 60 infants delivered by cesarean section or spontaneous vaginal delivery. Hypoglycemia was defined as a blood glucose level of < 40 mg/dL. This study disclosed a 43% incidence of hypoglycemia in C-section infants and 37% incidence in vaginally delivered infants. Neonates who are black, male, or both had a higher incidence of hypoglycemia. Other prenatal or intrapartal factors were not significantly associated with the development of hypoglycemia. As the incidence of hypoglycemia was much higher than previous studies the author suggested that further investigation of the affects of conduction anesthesia on blood glucose levels should be done. | II-2 |
| Swenne I, Ewald U, Gustafsson J, Sandberg E, Ostenson CG. Inter-relationship between serum concentrations of glucose, glucagon and insulin during the first two days of life in healthy newborns. **Acta Paediatr** 1994; 83(9):915-919 | Normal breastfed newborns had blood samples taken on day 0 (3-15 hr) and day 1 (24 hrs later) and analyzed for serum glucose, glucagons and insulin. Serum glucose increased with postnatal age and was inversely proportional to serum glucagons. Insulin levels did not change over time and were not correlated with serum glucose. | II-2 |
| Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 hrs of life. **J Pediatr** 1987; 110(1):119-122 | This study attempted to define normal values of serum glucose during the first 48 hours of life in well term neonates cared for according to the current standards and to compare serum glucose levels in breastfed and bottle fed infants during that period. Please note these were the infant feeding standards as of 1987 which included scheduled feedings at 2 hours and then 5 – 6 hours and then subsequently according to nursery routine which was 1, 5 and 9 am, and 1, 5 and 9pm. Breastfed infants were often offered feedings of dextrose water or formula after nursing. Interestingly the breastfed infants fed in this manner had twice the weight loss of the bottle fed infants. The single maternal serum glucose level was collected within 30 minutes of delivery and infant blood samples were obtained from the cord blood, and by heelstick at 1 hour, 2 hours, 3 – 4 hours after the first feeding and 3 – 4 hours after three subsequent feedings with the last sample being between 44 and 52 hours of life. Statistically significant differences were found between serum glucose levels of breastfed (lower) and bottle fed groups at 5 – 6, and 44 – 52 hours of life. On the basis of their findings they recommended that | II-2 |

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| | hypoglycemia in full term infants be defined as a serum glucose concentration of < 30 mg/dL on the first day of life or < 40 mg/dL in the second day of life. | |
| Cahill JB, Martin KL, Hulsey TC, Wagner CL. Incidence of hypoglycemia in term large for gestational age (LGA) infants as a function of enteral feeding type. Abstract PL8, Academy of Breastfeeding Medicine Annual International Meeting, Nov 14-17, 2002, Vancouver, BC, Canada | The perinatal database of an urban university nursery service was screened from January 1, 1996 – December 31, 2000 for all inborn births 37 – 45 weeks being large for gestational age based on birth weight for gestational age by Dubowitz exam. Patients with significant risk factors for hypoglycemia were excluded. The diagnosis of hypoglycemia was < 40 mg/dL on newborn screening protocol. These patients were then stratified by type of neonatal nutrition: breastfed, formula fed, breastfed switched to formula feeding or both, and formula feeding switched to breastfeeding or both. Of 757 newborns eligible for inclusion, 97% were normoglycemic and 3% experienced hypoglycemia (< 40 mg/dL). LGA newborns without other risk factors for hypoglycemia had no significant difference in the incidence of hypoglycemia for initial breastfeeding (3.6%) and initial formula feeding (3.3%). This study encouraged the use of breastfeeding in presumed healthy LGA newborns as the optimal nutrition source. | II-3 |
| Anderson S. Shakya KN, Shrestha LN, Costello AM. Hypoglycaemia: a common problem among uncomplicated newborn infants in Nepal. **J Trop Pediatr** 1993; 39(5):273-7 | A cross-sectional sample (stratified by weight and age after birth) was done on 226 uncomplicated term newborns from the delivery and post natal wards of a busy government maternity hospital in Kathmandu. The definition of hypoglycemia was a corrected blood glucose < 2.6 mmol/L during the first 50 hours after birth. The incidence of hypoglycemia was 38%. An additional 31 infants were studied longitudinally during the same period and 87% had at least one blood glucose measurement < 2.6 mmol/L and 81% had a rectal temperature < 35.5°C. Hypothermia, young maternal age, low birth weight and early sampling after birth were independent risk factors for hypoglycemia. | II-3 |
| Srinvasan G, Phildes RS, Cattamanchi G et al. Plasma glucose values in normal neonates: a new look. **J Pediatr** 1986; 109: 114-17 | Full term infants born at Cook County Hospital between January and June 1983 who weighed between 2500-4000 grams and were appropriate weight for gestational age were included in the study. Nursery routines at that time were to admit all neonates to an observation nursery. The infants were then placed under a servo controlled radiant warmer. Skin care and bath were given after stabilization of the core temperature. All infants were fed 20 calorie per ounce formula starting at 3 to 4 hours of age. After feeding the infants were transferred to their respective nurseries and fed every four hours. Only 10-15 % of the infants were actually breastfed. Serial samples were drawn of one group of 60 neonates from mixed arteriovenous cord blood and at 1, 2, and 3 hours after birth until the first feeding. Additional cross sectional samples were taken from 284 infants and collected at 4, 6, 12-24, 25-48, 49-72, 73-96, 97-168 hours of age before the routine morning feeding. Mean cord plasma glucose values in infants delivered vaginally were significantly lower than those born by cesarean section. The nadir plasma glucose concentrations were reached between 1 and 2 hours of | II-3 |

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| | birth with a significant increase over the one hour value seen by 3 hours which was unrelated to feedings as feedings were not started until 3-4 hours of age. | |
| Nicholl R. What is the normal range of blood glucose concentrations in healthy term newborns? **Arch Dis Child** 2003; 88:238-9 | Structured clinical question with brief, recent literature search and clinical bottom line: 1. The normal range of blood glucose is around 1.5-6 mmol/L per liter in the first days of life, depending on the age of the baby, type of feed, assay method used, and possibly mode of delivery. 2. Up to 14% of healthy term babies may have blood glucose < 2.6 mmol/L in the first 3 days of life. Lowest concentrations are more likely on day 1. 3. There is no reason to routinely measure blood glucose in AGA term babies who are otherwise well. "Jitteriness" is mostly a benign finding. 4. Feeding difficulty should be overcome with education, promotion, and support for breastfeeding. | III |
| Kalhan S, Peter-Wohl S. Hypoglycemia: what is it for the neonate? **Am J Perinatol** 2000; 17(1):11-18 | Review of the literature regarding definition of hypoglycemia and recommendations. "Hypoglycemia in the neonate should be evaluated in relation to (a) age of manifestation, (b) its duration, whether transient or persistent, and (c) whether or not it is associated with clinical symptoms. In clinically symptomatic infants, plasma glucose of ≤ 45 mg/dL (2.5 mmol/L) should be considered threshold for intervention. In an asymptomatic, at risk infant, plasma values ≤ 36 mg/dL (2.0 mmol/L) should be considered threshold. Breastfed infants tend to have lower blood glucose and higher ketone bodies, so the numbers could be adjusted somewhat. Targeted therapeutic values should be 72-90 mg/dL (4-5 mmol/L). | III |
| Schwartz RP. Neonatal hypoglycemia: How low is too low? Editorial. **J Pediatr** 1997; 131:171-3 | Editorial discussion of the difficulty in defining abnormal glucose concentrations in plasma and serum and related hyperinsulinism with reference to a study by Katz et al Journal of Pediatrics 1997; 131:193 -9. That study reported that low insulin-like growth factor binding protein-1 levels in serum may be a marker for hyperinsulinism. | III |
| Sinclair JC. Approaches to the definition of neonatal hypoglycemia. **Acta Paediatr Jpn** 1997; 39(Suppl 1):S17-S20 | Review of various approaches to the definition of neonatal hypoglycemia. The data correlating neonatal hypoglycemia with neurological outcome are limited because of a lack of suitable non-hypoglycemic controls, a failure to consider other pathology, and the small number of asymptomatic infants followed. | III |
| Sexson WR. Incidence of neonatal hypoglycemia: a matter of definition. Editorial. **J Pediatr** 1984; 105(1):149-150 | Editorial stressing that the incidence of "hypoglycemia" depends on the criteria for diagnosis. | III |
| **Long-Term Outcomes of Hypoglycemia** | | |
| Yager JY, Heitjan DF, Towfighi J, Vannucci RC. Effect of insulin-induced and fasting hypoglycemia on | Seven day postnatal rats were rendered hypoglycemic either by receiving a subcutaneous injection of insulin or by fasting for 12 hours. All rat pups | I |

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| perinatal hypoxic-ischemic brain damage. **Pediatr Res** 1992; 31: 138-42 | underwent unilateral common carotid artery ligation followed by exposure to 8% oxygen balance nitrogen at 37°C for 2 hours. Control animals (no insulin or fasting) received subcutaneous injections of normal saline. Mean blood glucose concentrations were 5.4, 4.3 and 3.4 mmol/L for control, insulin, and fasted animals respectively. Blood beta-hydroxybutyrate concentrations were identical for control and insulin treated animals, but more than doubled in concentration for the fasted animals. Mortality rates during hypoxia-ischemia where higher in the insulin treated animals (30%) than in either the fasted (4%) or control (0%) animals. Fasted animals showed a significant reduction in hypoxic-ischemic brain damage as compared with either the insulin treated or control animals. The findings indicated that fasting adequate to produce hypoglycemia and ketonemia improve neuropathologic outcome. | |
| Dalgic N, Ergenekon E, Soysal S, Koc E, Atalay Y, Gucuyener K. Transient neonatal hypoglycemia – long-term effects on neurodevelopmental outcome. **J Pediatr Endocrinology & Metabolism**. 2002; 15(2):319-324 | Report of 94 infants with hypoglycemia (defined as blood glucose < 2.2 mmol/L [40 mg/dL]) admitted to a university NICU from March 1998 to December 2000 (2.33% of live births, and 9.18% of NICU admissions). Cause, duration of treatment and outcome for varying time periods up to 24 months were recorded. 20% has maternal diabetes, 36 % were premature, and 14% were both. 1 preterm infant had an insulinoma, one infant had hypoxic-ischemic encephalopathy, 1 infant was SGA and 27% had no known risk factors. Of the 48 infants followed at some time between 6 and 24 months, only 3 had minor neurodevelopmental problems and no major defect was identified. | II-2 |
| Duvanel CB, Fawer CL, Cotting J, Hohlfeld P, Matthieu JM. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational age preterm infants. **J Pediatr** 1999; 134:492-498 | 85 small for gestational age pre-term infants were evaluated prospectively and grouped according to their glycemic status. Hypoglycemia was defined as < 2.6 mmol/L (47mg/dL). The incidence of hypoglycemia was 72.9%. Infants with repeated episodes of hypoglycemia had significantly reduced head circumferences and lower scores in specific psychometric tests at 3.5 years of age. They concluded that recurrent episodes of hypoglycemia were strongly correlated with persistent neuro-developmental and physical growth deficits until 5 years of age. Recurrent hypoglycemia also was a more predictable factor for long term effects than the severity of a single hypoglycemic episode. Therefore repetitive blood glucose monitoring and rapid treatment even for mild hypoglycemia were recommended in small for gestational age infants in the neonatal period. | II-2 |
| Kinnala A, Rikalainen H, Lapinleimu H, Parkkola R, Kormano M, Kero P. Cerebral magnetic resonance imaging and ultrasonography findings after neonatal hypoglycemia. **Pediatrics** 1999; 103(4):724-729 | Eighteen symptomatic full term infants whose serum glucose concentrations were ≤ 45 mg/dL (2.5 mmol/L) without any other diseases were included in a "hypoglycemic group". MRI and head ultrasound scans were performed at full term age and at the age of 2 months. The imaging studies were compared with the findings of MRI and ultrasound scans on 19 healthy, normo-glycemic term newborns infants at their respective ages. Postnatal full term MRI and ultrasound scans showed abnormalities four times more often after transient neonatal | II-2 |

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| | hypoglycemia than in the healthy control group. However most lesions were absent 2 months later. The abnormal findings on the initial head ultrasounds and MRI scans were quite varied. | |
| Koivisto M, Blanco-Sequeiros M, Krause U. Neonatal symptomatic and asymptomatic hypoglycemia: a follow-up study of 151 children. **Develop Med Child Neurol** 1972; 14:603-614 | One hundred fifty one children diagnosed as having hypoglycemia during the first few days of life were followed up one to four years after birth. Of the 151 infants, 8 had hypoglycemia with convulsions and 77 had hypoglycemia without convulsions but with other symptoms. 66 had been asymptomatic. They found that symptomatic hypoglycemia with convulsions had a poor prognosis for permanent CNS damage, while asymptomatic hypoglycemia without convulsions appeared to have no sequelae. Of note is that the symptomatic convulsion group were older at age of diagnoses (39 hours) and had a duration of hypoglycemia that was longer than both the symptomatic non-convulsion group and the asymptomatic group. The definition of hypoglycemia used was < 30 mg/dL. A control group of 56 asymptomatic newborn infants was used. | II-2 |
| 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):2231-2243 | Systematic review of cohort studies on subsequent neurologic development after episodes of hypoglycemia in the first week of life. Of the eighteen eligible studies, the overall methodologic quality was considered poor in 16 studies and high in 2 studies. Pooling of the results of the 2 high-quality studies was deemed inappropriate because of major clinical and methodologic heterogeneity. None of the studies provided a valid estimate of the effect of neonatal hypoglycemia on neurodevelopment. Building on the strengths and weaknesses of existing studies, they proposed an "optimal" future study design and invited content experts and clinicians world-wide to comment and refine the design and participate in a prospective collaborative study. | II-3 |
| Alkalay AL, Flores-Sarnat L, Sarnat HB, Farber SJ, Simmons CF. Plasma glucose concentrations in profound neonatal hypoglycemia. **Clin Pediatr** 2006; 45(6):550-558 | Meta-analysis of 16 studies of infants with neurologic sequelae associated directly or primarily with profound hypoglycemia. Of 89 infants, more than 95% had plasma glucose levels < 25 mg/dL that were first detected at more than 10 hours of age. Based on their analysis, intervention and close monitoring is urgent when plasma glucose levels fall below 25 mg/dL. The incidence of significant neurologic sequelae in infants who have plasma glucose concentrations < 25 mg/dL for several hours was estimated to reach 21% (95% CI 14-27%). | II-3 |
| Filan PM, Inder TE, Cameron FJ, Kean MJ, Hunt RW. Neonatal hypoglycemia and cerebral injury. **J Pediatr** 2006; 148:552-555 | Case report of 4 infants with neonatal hypoglycemia and occipital cerebral injury on MRI and summary of previous reports. 2 of the 4 cases had hypoglycemic seizures, but only 1 had long term sequellae (microcephaly, gross motor delay and visual impairment). The other 3 infants had normal development and normal visual function at 9 months of age. The pattern of predominant occipital injury agrees with previously reported studies, but as yet there is no explanation for this pattern of injury. | II-3 |

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| Alkalay AL, Flores-Sarnat L, Sarnat HB, Moser FG, Simmons CF. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. **Clin Pediatr** 2005; 44(9):783-790 | Case report and review of 22 previously published cases (in English) of hypoglycemia with brain imaging. Abnormal brain imaging findings were associated with profound and prolonged hypoglycemia with involvement of the occipital lobes in 82% of affected newborns. Half of these infants had visual impairment. The median of plasma glucose values was 7 mg/dL (range 2-26 mg/dL) and median postnatal age when hypoglycemia was first detected was 48 hours (range 1-72 hours). | II-3 |
| Brand PLP, Molenaar NLD, Kaaijk C, Wierenga WS. Neurodevelopmental outcome of hypoglycemia in healthy, large for gestational age, term newborns. **Arch Dis Child** 2005; 90:78-81 | Screening for hypoglycemia was performed at 1, 3, and 5 hours after birth and continued if blood glucose levels were low. Low was defined as a plasma glucose < 2.2 mmol/L one hour after birth or < 2.5 mmol/L subsequently. Seventy-five healthy term large for gestational age infants born to non-diabetic mothers were screened and then followed up at four years of age for neuro-developmental outcome. They found that transient mild hypoglycemia in healthy term LGA newborns did not appear to be harmful to psychomotor development at age four years. There were no differences in any of the test scores between hypoglycemic children who had been treated with intravenous glucose or not. Unfortunately only 64% of the original population of LGA infants were able to be followed up at the age of 4 years. In their population none of their LGA newborns had evidence of recurrent hypoglycemia or evidence of hyperinsulinemia. Unfortunately, mode of feeding, whether breastfed, formula fed or mixed fed, was not elucidated. | II-3 |
| Koh THHG, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycemia. **Arch Dis Child** 1988; 63:1353-58 | Brainstem auditory evoked responses and somatosensory responses were measured in relation to blood glucose concentration in 17 children: 13 were fasted or given insulin to investigate metabolic abnormalities and 4 had spontaneous episodes of hypoglycemia. Abnormal evoked potentials where recorded in 10 of the 11 children whose blood glucose concentration fell below 2.6 mmol/L. Five of these 10 children were asymptomatic. Unfortunately only 5 of their subjects were less than one week of age. Four of their 5 infants had no symptoms and one was classified as drowsy. They concluded that the blood glucose concentration should be maintained above 2.6 mmol/L to insure normal neural function in children irrespective of the presence or absence of abnormal clinical signs. | II-3 |
| Rozance PJ, Hay WW. Hypoglycemia in newborn infants: Features associated with adverse outcomes. **Biol Neonate** 2006; 90(2):74-86 | Review article which tries to document from the literature values of blood/plasma glucose concentration and associated clinical signs and conditions in newborn infants (both term and preterm) that indicate a reasonable clinical probability that hypoglycemia is a proximate cause of acute and/or sustained neurological injury. They also review the physiological and pathophysiological responses to hypoglycemia that may influence the ultimate outcome of newborns with low blood glucose. They conclude that there is inadequate information in the literature to define any one value of glucose below which irreparable | III |

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| | hypoglycemic injury to the central nervous system occurs, at any one time or for any defined period of time, in a population of infants or in any given infant. | |
| Alkalay AL, Sarnat HB, Flores-Sarnat L, Simmons CF. Neurologic aspects of neonatal hypoglycemia. **Isr Med Assoc J** 2005; 7:188-192 | Excellent summary of the clinical conditions associated with hypoglycemia, neuropathologic findings (in comparison with hypoxic-ischemic encephalopathy), symptomatology, neurologic sequellae, neuro-imaging and function testing regarding hypoglycemic encephalopathy. | III |
| Yager JY. Hypoglycemic injury to the immature brain. **Clin Perinatol** 2002; 29:651-674 | Review of the definitions, incidence and pathophysiology of neonatal hypoglycemia with a view toward both short and long-term clinical and radiologic outcomes. Discusses normal compensatory mechanisms and the increased resistance of the neonatal brain to the effects of hypoglycemia. | III |
| Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. **Semin Neonatol** 2001; 6:147-155 | This review emphasizes the clinical, neuropathologic, and neuro-imaging features of hypoglycemia in newborn infants, especially those who are symptomatic. Experimental observations emphasize the resistance of the immature brain to the damaging effect of hypoglycemia. Such resistance occurs as a consequence of compensatory increases in cerebral blood flow, lower energy requirements, higher endogenous carbohydrate stores, and the ability to utilize alternative substrates to spare glucose for energy production. | III |
| Hawdon JM. Hypoglycemia and the neonatal brain. **Eur J Pediatr** 1999; 158(Suppl 1):S9-S12 | Literature review and synthesis of the neurologic effects of hypoglycemia, neuroprotective mechanisms, neurophysiologic changes and neurodevelopmental outcome of animals and humans subjected to hypoglycemia. "Evidence from studies of humans and other animals suggests that cortical damage and long-term sequellae occur after prolonged hypoglycemia sufficiently severe to cause neurologic signs." | III |
| **Risk Factors/Etiologies of Hypoglycemia** | | |
| Sasidharan CK, Gokul E, Sabitha S. Incidence and risk factors for neonatal hypoglycemia in Kerala, India. **Ceylon Medical Journal** 2004; 49(4):110-113 | 604 neonates were enrolled by a systematic random sampling method from August 1 to November 1, 2002 at a university hospital in Kerala, India. Random blood glucose levels were obtained using standard glucose oxidase-peroxidase method on two occasions 24 hours apart during the first 2 days of life. 19 clinical characteristics of the mother baby pair were analyzed statistically in relation to the occurrence of hypoglycemia (defined as blood glucose values < 2.2 mmol/L). The incidence of neonatal hypoglycemia was 41/1000 live births. Eight variables strongly and independently predicted the risk of neonatal hypoglycemia with at least one being present in 89.1% of the hypoglycemic neonates. These variables included prematurity, low birth weight, maternal diabetes mellitus, delay in initiation of breastfeeding for more than 2 hours post-natally, maternal preeclampsia and eclampsia, birth asphyxia, cold stress or hypothermia, and maternal oligohydramnios. As with other "modifiable" risk factors in the third world, both feeding delay and cold stress have been recognized as causative | II-2 |

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| | factors of neonatal hypoglycemia. | |
| Wang ML, Dover DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. **Pediatrics** 2004; 114(2): 372-376 | Retrospective case-control record review of 90 near-term and 95 full-term infants re clinical outcomes (temperature instability, hypoglycemia, respiratory distress, jaundice), length of stay and cost of care. Near-term infants had 3 times the incidence of hypoglycemia (defined as < 40 mg/dL) as full-term infants. | II-2 |
| Johnson TS. Hypoglycemia and the full-term newborn: how well does birth weight for gestational age predict risk? **JOGNN** 2003; 32(1):48-57 | Anthropometric measurements were obtained twice for each of 157 full term newborns (94 White and 63 African Americans) and correlated with risk of hypoglycemia (defined as ≤ 40 mg/dL) using an Accu-Check III glucose reflectance monitor at 2 hours of age or earlier if the newborn demonstrated signs of hypoglycemia. As expected, there were statistically significant differences by race in weight, head circumference, chest circumference, abdominal circumference, mid arm circumference and length measurements, and by gender in head circumference and thigh circumference measurements. Newborns with a mid-arm circumference/head circumference ratio that varied from .26 to .29 (the "thinner" infants) had an odds ratio of 6.10 for risk of hypoglycemia. Plotting a newborn's birth weight on a published fetal growth curve clearly did not accurately predict his or her risk of hypoglycemia. | II-2 |
| Holtrop PC. The frequency of hypoglycemia in full-term large and small for gestational age newborns. **Am J Perinatol** 1993; 10(2):150-154 | Bedside test strip blood glucose values were determined on 298 full term LGA and 204 full term SGA newborns at 1, 2, 3, 6, 12, 24, 36 and 48 hours of age. Mothers were not diabetic. Serum glucose determination was immediately done if a test strip reading was <40 mg/dL. Hypoglycemia was defined as a serum glucose < 35 mg/dL at less than 3 hours of age, < 40 mg/dL at 3-24 hours of age, < 45 mg/dL at more than 24 hours of age. The frequency of hypoglycemia in LGA infants was 8.1% and in SGA infants 14.7%. The mean age at which hypoglycemia occurred was 2.9 hours in LGA infants and 6.1 hours in SGA infants. Their recommendations were that screening for hypoglycemia in LGA infants whose mothers were not diabetic may be stopped after 12 hours but should continue for 48 hours in SGA infants. | II-2 |
| Schaefer-Graf UM, Rossi R, Buhrer C, Siebert G, Kjos S, Dudenhausen JW, Vetter K. Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of non-diabetic mothers. **Am J Obstet Gynecol** 2002; 187:913-917 | Retrospective chart review of LGA infants of nondiabetic mothers between 1994 and 1998. Hypoglycemia (defined as ≤ 30 mg/dL) occurred in 16% of 887 LGA infants, decreasing with increasing age in hours after birth. The mother's 1-hr glucose value of an oral glucose tolerance test was a fairly good predictor of subsequent neonatal hypoglycemia. Routine glucose testing was recommended for LGA infants of non-diabetic mothers. | II-3 |
| de Lonlay P, Giurgea I, Touati G, Saudubray J-M. Neonatal hypoglycaemia: aetiologies. **Seminars in Neonatology** 2004; 9:49-58 | Review of the etiologies of hypoglycemia in the newborn by basic endocrine/metabolic pathways. | III |
| Sunehag AL, Haymond MW. Glucose extremes in newborn infants. **Clin Perinatol** 2002; 29:245-260 | Review of pathophysiology of transition from fetal to neonatal life and of various causes of neonatal hypo- and hyperglycemia. | III |

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| Stanley CA, Baker L. The causes of neonatal hypoglycemia, Editorial. **NEJM** 1999; 3040:1200-1201 | Editorial comment reviewing congenital metabolic and endocrine disorders associated with hypoglycemia and declaring maintaining plasma glucose above 60 mg/dL (3.3 mmol/L) as the therapeutic goal. | III |
| **Clinical Manifestations of Hypoglycemia** | | |
| Groenendaal F, Elferink-Stinkens PM. Hypoglycemia and seizures in large-for-gestational-age (LGA) full-term neonates. **Acta Paediatr** 2006; 95(7):874-876 | Analysis of data from the Netherlands Perinatal Registry. From 1997 to 2002 hypoglycemia [defined as plasma glucose < 2.5 mmol/L (< 45 mg/dL)] was recorded in 1513 of 9318 (16.2%) admitted LGA full-term neonates without diagnosed maternal diabetes, of whom 20 (1.3%) had seizures. In 6 of the 20, hypoglycemia was the single cause of the seizures. They concluded that symptomatic hypoglycemia can occur in healthy, LGA full-term neonates. | II-3 |
| Moore AM, Perlman M. Symptomatic hypoglycemia in otherwise healthy, breastfed term newborns. **Pediatrics** 1999; 103:837-839 | This is a case series report of 3 apparently full term infants with no recognized perinatal risk factors for hypoglycemia who presented at home on day 3 of life with seizures or life threatening apneas due to neonatal hypoglycemia. Of note in the cases were that two of the three mothers were primiparous and all three infants were breastfeeding poorly at the time of discharge. Initial neuro-imaging including CT and ultrasound were abnormal in all three infants. Two of the three infants are subsequently normal with one delayed in a special school. Blood glucose values were from 9 – 23 mg/dL upon re-admission at three days of age. All three of the infants had no urinary ketones suggesting a defective ketogenic response to critically low blood glucose values. | II-3 |
| Plus see many review articles. | | |
| **Management Recommendations** | | |
| McGowan JE, Perlman JM. Glucose management during and after intensive delivery room resuscitation. **Clin Perinatol** 2006; 33(1):183-96 | The evidence regarding the role of glucose in modifying post-asphyxial brain injury and resuscitation is reviewed to better define optimal glucose management after perinatal asphyxia and resuscitation. | III |
| No authors listed. Management of asymptomatic hypoglaecemia in healthy term neonates for nurses and midwives. **Aust Nurs J** 2006; 13(11):32-35 | Review and recommendations for diagnosis and management of hypoglycemia in healthy, full term infants. | III |
| Williams AF. Neonatal hypoglycaemia: clinical and legal aspects**. Semin Fetal Neonatal Med** 2005; 10(4):363-8 | Review article noting that transiently low blood glucose levels are a normal feature of adaptation to extrauterine life, and that there is no evidence that this causes brain injury in the absence of concurrent clinical manifestations. No single concentration of plasma glucose can be associated universally with either the appearance of clinical signs or causation of cerebral injury. Treatment should be based on "operational thresholds" and guided by clinical assessment, not absolute glucose values. | III |

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| American Academy of Pediatrics, Section on Breastfeeding, Policy Statement: Breastfeeding and the Use of Human Milk. **Pediatrics** 2005; 115(2):496-506 | Extensive review and recommendations re breastfeeding and the use of human milk. No supplementation without medical indication. | III |
| Bhutta ZA, Darmstadt GL, Haws RA. Community-based interventions for improving perinatal and neonatal health outcomes in developing countries: a review of the evidence. **Pediatrics** 2005 Feb; 115(2): Supplement pg574-576 | "The most cost-effective strategy for preventing hypoglycemia is early feeding (continued every 2-3 hours on demand day and night) with breastmilk, which is superior to milk formula in that it can promote relatively greater ketogenesis and has a relatively lower insulinogenic effect..…. Thus, consonant with the recommendations of the WHO, the mainstay of prevention and treatment of hypoglycemia in developing countries must clearly remain early and exclusive breastfeeding and the use of expressed breastmilk in other circumstances." | III |
| American Academy of Pediatrics & American College of Obstetricians & Gynecologists. **Guidelines for Perinatal Care**, 5th Ed. American Academy of Pediatrics, 2002, pg 207 | "In the absence of risk factors and symptoms, screening for….. hypoglycemia by blood glucose screening… is not warranted. Screening for blood glucose and hematocrit abnormalities is appropriate for high-risk neonates, such as those born to mothers who have diabetes mellitus and in cases of intrauterine growth restriction and twin-to-twin transfusion." | III |
| Alkalay AL, Klein AH, Nagel RA, Sola A. Neonatal non-persistent hypoglycemia. **Neonatal Intensive Care** 2001; 14(2):25-34 | Review of clinically relevant literature related to the definition, clinical symptomatology, methodologies for blood glucose determination, and physiology of neonatal hypoglycemia. They propose a working definition of hypoglycemia based on age post birth, and a clinical pathway for management of neonatal non-persistent hypoglycemia. | III |
| Haninger NC, Farley CL. Screening for hypoglycemia in healthy term neonates: effects on breastfeeding. **J Midwifery & Women's Health** 2001; 46(5):292-301 | Review of the literature and exploration of the potential adverse sequelae of inappropriate glucose screening in healthy breastfeeding newborns. Routine glucose screening of the term healthy neonate is not an evidence-based clinical practice, and serves as a significant detriment to successful breastfeeding behaviors. | III |
| Cornblath M, Ichord R. Hypoglycemia in the neonate. **Sem Perinatol** 2000; 24(2):136-149 | A review article encompassing the history, pathogenesis, and pathophysiology, risk factors, definitions, and methodological issues in glucose measurement associated with neonatal hypoglycemia. Whipple's triad is described along with a discussion of epidemiologic, physiologic, and outcome definitions of hypoglycemia. A proposed definition of neonatal hypoglycemia encompassing "operational thresholds" as an indication for action, and not a diagnosis of disease, is described. An algorithm for action is presented as well as a brief discussion of recurrent or persistent neonatal hypoglycemia. | III |
| National Childbirth Trust, United Kingdom. Hypoglycemia of the Newborn: Guidelines for appropriate blood glucose screening and treatment of breast-fed and bottle-fed babies in the UK. **Midwives** 1997 Oct; 110(1317):248-9 | Evidence-based guidelines for appropriate glucose screening and treatment of both breastfed and bottle-fed infants in the United Kingdom. 1. Early and exclusive breastfeeding meets the nutritional needs of healthy term newborns. 2. Such babies need not be screened for hypoglycemia and need no supplementary feeds. 3. Breastfeeding should be initiated when the infant is ready, preferably within an hour of birth. Skin-to-skin care should be used to facilitate | III |

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| | breastfeeding and maintain temperature. 4. Breastfeeding should continue as the baby demands. Long intervals between feeds does not harm normal newborns. 5. The infant who is unwilling to feed or does not wake may be ill and needs an examination, not just glucose screening. 6. These guidelines do not apply to ill, premature, SGA or IDM infants. 7. Healthy term infants do not develop symptomatic hypoglycemia as a consequence of underfeeding. Underlying illness should be excluded. The blood glucose in infants with clinical signs should be kept > 2.6 mmol/L per liter. | |
| Hawdon JM, Ward Platt MP, Aynsley-Green A. Prevention and management of neonatal hypoglycemia. **Arch Dis Child Fetal Neonatal Ed** 1994; 70:F60-F65 | Review of the metabolic adaptation regarding glucose in healthy term, preterm and SGA infants as well as those with hyperinsulinism and perinatal asphyxia. An algorithm is presented for prevention and management of hypoglycemia in fed and unfed infants. A clear statement is made that monitoring of blood glucose concentrations in healthy, AGA term infants is "unnecessary and potentially harmful to parental well-being and the successful establishment of breast feeding." | III |
| Mehta A. Prevention and management of neonatal hypoglycaemia. **Arch Dis Child** 1994; 70:F54-F65 | Explanation of the normal and abnormal metabolic transitions from fetus to newborn with recommendations for treatment of specific groups of neonates (term, IDM, preterm). Caution is requested regarding glucose boluses which inhibit glucagon secretion and prolong the glucose instability. | III |
| AAP Committee on Fetus and Newborn, American Academy of Pediatrics. Routine Evaluation of Blood Pressure, Hematocrit, and Glucose in Newborns. **Pediatrics** 1993;92(3):474-76 | There is no evidence that asymptomatic hypoglycemic infants will benefit from treatment. Recommendation not to screen healthy term newborns for hypoglycemia, only infants with significant risk factors. | III |
| Hawdon JM. Neonatal hypoglycemia: the consequences of admission to the special care nursery. **Child Health** 1993; Feb: 48-51 | Review of the definitions of hypoglycemia and consequences of unnecessary routine screening in terms of maternal-child separation and interference with breastfeeding. | III |
| Hawdon JM, Ward Platt MP, Aynsley-Green A. Neonatal hypoglycemia - blood glucose monitoring and infant feeding. **Midwifery** 1993; 9: 3-6 | This is a review of the definition of neonatal hypoglycemia along with implications for feeding practices. They conclude that term babies, especially those who are breastfed, are prone to low blood glucose concentrations in the first 2 to 3 days after birth. However, as they are able to generate ketone bodies, which are used as alternative fuels for the brain, it is likely that this has no clinical implication for otherwise healthy and asymptomatic babies. Therefore, they recommend there should be few occasions on which blood glucose concentrations need to be measured. Unless the baby becomes clinically dehydrated or has symptoms of hypoglycemia he/she does not need to be woken for feeds or have breastfeeds complimented with artificial milk. They note the situation is quite different for preterm or SGA babies for whom an adequate calorie supply should be ensured. However even in this group of infants glucose homeostasis may be | III |

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| | achieved by frequent breastfeeds with artificial compliments until full breastfeeding is established. | |
| **Point-of-Care Testing** | | |
| Piper HG, Alexander, JL, Shukla A, Pigula F, Costello JM, Laussen PC, Jaksic T, Agus MS. Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. **Pediatrics** 2006; 118(3):1176-1184 | Twenty children up to 36 months who were undergoing cardiac bypass surgery had a subcutaneous continuous glucose monitor placed after induction for a maximum of 72 hrs. Values correlated well with laboratory glucose values. All patients tolerated the sensors well without bleeding or tissue reaction. Body temperature, inotrope dose and body-wall edema did not affect the readings. | II-3 |
| Beardsall K, Ogilvy-Stuart AL, Ahluwalia J, Thompson M, Dungar DB. The continuous glucose monitoring sensor in neonatal intensive care. **Arch Dis Child Fetal Neonatal Ed** 2005; 90:F307-F310 | Continuous glucose monitoring via subcutaneous glucose sensors (disposable, glucose oxidase based, platinum electrode) were well tolerated with readings comparable to those on point-of-care whole blood monitors. Patients were 16 preterm infants <1500 g at birth studied from within 24 hrs of delivery and for up to 7 days. | II-3 |
| Hamid MH, Chishti AL, Maqbool S. Clinical utility and accuracy of a blood glucose meter for the detection of neonatal hypoglycemia. **J Coll Physicians Surg Pak** 2004; 14(4):225-8 | The Accutrend Alpha Glucometer was compared with standard laboratory glucose measurement by the hexokinase method in a total of 292 paired of samples taken from 223 neonates in the neonatal unit of Children's Hospital Lahore Pakistan from August 2001 to February 2002. Hypoglycemia (defined as <40 mg/dL) was found in 38.4% of the samples. They found the instrument used showed a sensitivity of 98% and specificity of 93% to detect neonatal hypoglycemia as defined, with a positive predictive value of 88% and a negative predictive value of 99%. Their conclusion was that the blood glucose reflectance meter could be a useful and accurate instrument for screening and detecting neonatal hypoglycemia in symptomatic babies under stress. They stressed however that all low values by glucometers should be promptly analyzed and confirmed by laboratory glucose measurement. | II-3 |
| Ho HT, Yeung WKY, Young BWY. Evaluation of "point-of-care" devices in the measurement of low blood glucose in neonatal practice. **Arch Dis Child Fetal Neonatal Ed** 2004; 89:F356-F359 | Five readily available glucometers were evaluated in comparison with true plasma glucose measured in the laboratory. None of the five glucometers were satisfactory as the sole measuring device with highly varying sensitivity and negative predictive values. Confirmation with laboratory measurements plasma glucose in clinical assessment are still of the utmost importance when diagnosing neonatal hypoglycemia. | II-3 |
| Schlebusch H, Niesen M, Sorger M, Paffenholtz I, Fahnenstich H. Blood glucose determinations in newborns: four instruments compared. **Pediatr Pathol Lab Med** 1998; 18(1):41-8 | Four portable analyzers, HemoCue B-Glucose, Accu-Check 3, One-Touch II, and Glucometer Elite with differing measuring principles were tested for their suitability for measuring blood glucose in neonates. All devices showed an influence of hematocrit, the magnitude of which varied from 5 to 12% for every 10% change in hematocrit. Two instruments revealed that temperature had a marked influence on the readings. Only one instrument (the HemoCue B-Glucose) met the requirements for accurate and precise blood glucose | II-3 |

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| | determination in neonates. | |
| Martin S, Jensen R, Daly L, Jergenson C, Johnson MB, Buell T. Comparison of two methods of bedside blood glucose screening in the NICU: evaluation of accuracy and reliability. **Neonatal Network** 1997; 16(2):39-43 | 100 samples were obtained from a convenience sample of 38 NICU infants (EGA 24-37 wks, aged 1-30 days) and run on both Chemstrip bG reagent strips and the One Touch II bedside glucose meter. 63% of the samples were compared with true serum glucose values, adjusted 10% for whole blood vs. serum glucose. The One-Touch method appeared more reliable (r=.92) than the Chemstrip bG method (r=.87), especially when the One Touch meter was not operated in the neonatal mode. | II-3 |
| Sharief N, Hussein K. Comparison of two methods of assessment of whole blood glucose in the neonatal period. **Acta Paediatr** 1997; 86(11):1246-52 | This study compared the performance and accuracy of the HemoCue B-glucose photometer system and reagent strip tests used in conjunction with reflectance photometry against a reference plasma glucose method. They found the limits of agreement of both methods compared with plasma glucose were too wide to be clinically acceptable in the neonatal period. | II-3 |
| Ellis M, Manandhar DS, Manandhar N, Land JM, Patel N, de L Costello AM. Comparison of two cotside methods for the detection of hypoglycemia among neonates in Nepal. **Arch Dis Child Fetal Neonatal Ed** 1996; 75(2): F 122-5 | This study compared two cot-side methods of blood glucose measurement (HemoCue and Reflolux II) against a standard laboratory glucose oxidase for the detection of neonatal hypoglycemia in Kathmandu, Nepal. In this study, although more accurate than Reflolux II for the measurement of blood glucose in mothers, HemoCue over-read the glucose concentrations in neonates and was therefore thought potentially dangerous as a screening method for neonatal hypoglycemia. The Reflolux II was felt useful as a screening method for high-risk infants. | II-3 |
| Sirkin A, Jalloh T, Lee L. Selecting an accurate point-of-care testing system: clinical and technical issues and implications in neonatal blood glucose monitoring. **JSPN** 2002; 7(3):104-112 | Detailed description of the range of bedside glucose testing systems, review of considerations in system selection, and how to implement studies to validate accuracy and precision of any glucose monitoring system. | III |
| Baird PB. Neonatal glucose screening. **Neonatal Network** 1996 Oct; 15(7):63-66 | Brief review of neonatal glucose screening with indications, sampling technique, methodology, reliability and clinical implications. There is a nice summary table of risk factors for hypoglycemia and also signs and symptoms of hypoglycemia. | III |

**Suggestions for Future Research**

1. Well-planned, well-controlled studies are needed that look at plasma glucose concentrations, clinical symptoms, and long-term sequelae so the levels of glucose necessary for intervention can be better understood.
2. The development of more reliable bedside testing methods would increase the efficiency of diagnosis and treatment of significant glucose abnormalities.
3. A clearer understanding of the role of other glucose-sparing fuels and methods to measure them in a clinically meaningful way and time frame would aid in understanding which babies are truly at risk of neurologic sequelae, and thus must be treated.
4. A determination of how much enteral glucose in what form is necessary to raise blood glucose to acceptable levels.

**SUMMARY:**

Healthy, full-term infants are programmed to make the transition from their intrauterine constant flow of nutrients to their extra-uterine intermittent nutrient intake without the need for metabolic monitoring or interference with the natural breastfeeding process. Homeostatic mechanisms ensure adequate energy substrate is provided to the brain and other organs, even when feedings are delayed. The normal pattern of early, frequent, and exclusive breastfeeding meets the needs of healthy full-term infants. Routine screening or supplementation are not necessary and may harm the normal establishment of breastfeeding. At-risk infants should be screened, followed as needed and treated with IV glucose if symptomatic or suggested thresholds are reached. Bedside screening is helpful, but not always accurate and should be confirmed with laboratory glucose measurement. Hypoglycemic encephalopathy and poor long-term outcome are extremely unlikely in asymptomatic infants and are more likely in symptomatic infants with persistent or repeated severe hypoglycemia episodes. A single low glucose value is not associated with long-term neurological abnormalities.

***US Preventive Services Task Force Ranking of Evidence from Scientific Studies**

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| I | Evidence obtained from at least one properly randomized controlled trial. |
| II-1 | Evidence obtained from well-designed controlled trials without randomization. |
| II-2 | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. |
| II-3 | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could be regarded as this type of evidence. |
| III | Opinions of respected authorities, based on clinical experience, descriptive studies and case reports; or reports of expert committees. |

The Academy of Breastfeeding Medicine, Inc.
February 2007

The Academy of Breastfeeding Medicine Protocol Committee
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