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## Screening guidelines for newborns at risk for low blood glucose

Despite decades of scientific observation, investigation and discussion, there is limited evidence-based consensus regarding the screening and management of infants at risk for neonatal hypoglycemia. A number of questions remain unresolved:

- How is neonatal hypoglycemia defined?
- Who is at risk for neonatal hypoglycemia?
- When should at-risk infants be screened?
- How should screening for neonatal hypoglycemia be performed?
- What levels of blood glucose require intervention?
- What interventions should be offered when neonatal hypoglycemia is suspected?
- How frequently should asymptomatic, at-risk infants be screened?
- How should caregivers be educated or counselled regarding screening for neonatal hypoglycemia?

**Table 1**  
**Levels of evidence**

Level of evidence	Type of study
1a	Systematic review of randomized controlled trials
1b	Individual randomized controlled trial (with narrow confidence interval)
1c	All cases affected before intervention, some or none affected after intervention
2a	Systematic review of cohort studies
2b	Individual cohort study (including low-quality randomized controlled trial)
2c	'Outcomes' research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

*Adapted with permission from reference 1*

Given the paucity of evidence, the purpose of the present statement is to provide a consensus guideline that has practical applications for Canadian newborns and their caregivers. An algorithm has also been developed to give direction in managing infants at risk for neonatal hypoglycemia. An information sheet has been appended for parents and other caregivers (pages 731-732). It should be noted that this guideline is a pragmatic approach, one that will require refinement as further scientific data become available.

### SEARCH STRATEGY

A MEDLINE search was performed for studies up to March 2004 using the key words "Hypoglycemia", "Blood Glucose" and "All Infant: birth-23 months", limited to "Human", "English" and "French", and including all trials, reviews, clinical practice guidelines, follow-up studies and meta-analyses. The Cochrane Database was searched for reviews and articles relating to glucose and infant feeding. It is noteworthy that no randomized clinical trials were found relating to strategies for screening for neonatal hypoglycemia in at-risk infants. All case-control and cohort studies were reviewed. Levels of evidence and grades of recommendations (Tables 1 and 2) were assigned according to the Oxford Centre for Evidence-Based Medicine guidelines (1).

### HOW IS NEONATAL HYPOGLYCEMIA DEFINED?

Neonatal hypoglycemia cannot be defined by a single value of glucose applicable to all clinical situations and to all

**Table 2**  
**Grades of recommendation**

Grade of recommendation	Levels of studies
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

*Adapted with permission from reference 1*

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**Table 3**  
**10th and 90th percentile cut-offs for birthweight at term in Canadian infants**

Gestation (completed weeks)	Birthweight (g)			
	10th percentile		90th percentile	
	Male	Female	Male	Female
37	2552	2452	3665	3543
38	2766	2658	3877	3738
39	2942	2825	4049	3895
40	3079	2955	4200	4034
41	3179	3051	4328	4154
42	3233	3114	4433	4251

*Adapted with permission from reference 18*

infants. It appears that infants may develop signs suggestive of hypoglycemia over a range of blood glucose levels that is substantially lower than normal adult levels.

“In approximate order of frequency there are jitteriness or tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak or high-pitched cry, limpness or lethargy, difficulty in feeding, and eye rolling. Episodes of sweating, sudden pallor, hypothermia, and cardiac arrest and failure also occur. There is frequently a clustering of episodic symptoms. Because these clinical manifestations may result from various causes, it is critical to measure serum glucose levels and to determine whether they disappear with the administration of sufficient glucose to raise the blood sugar to normal levels; if they do not, other diagnoses must be considered” (2).

So-called ‘normal ranges’ are presumably dependent on the infant’s size, gestation and clinical condition, as well as the availability of energy sources and ongoing energy demands. Definitions of hypoglycemia should be flexible enough to encompass all of these groups.

There are three approaches to defining a safe range for blood glucose (3):

1. **Using normative ranges:** Studies of exclusively breastfed, appropriate-for-gestational-age, term babies, show that blood glucose falls immediately after birth from two-thirds of maternal levels to the 5th percentile of approximately 1.8 mmol/L at 1 h of age (Level 2b) (4,5). There is a subsequent rise to levels over 2.0 mmol/L that is maintained for 72 h (6). It is important to note that 12% to 14% of normal, appropriate-for-gestational-age, breastfed newborns have a blood glucose level of less than 2.6 mmol/L in the first three days of life (7).
2. **Using the presence or absence of sequelae:** A number of studies in at-risk term, preterm and small-for-gestational-age (SGA; weight at less than the 10th percentile) infants have suggested an association of blood glucose levels of less than 2.6 mmol/L with abnormal short- (Level 4) and long-term neurological (Level 2a) or neuroimaging changes (Level 4) (2,8-14). Data from infants of diabetic mothers (IDMs) suggest

that long-term outcome may be negatively affected at lower levels (less than 1.6 mmol/L). Unfortunately, given the wide range of normal blood glucose levels found in newborns and the variety of causes of low blood glucose, cohort and case-control studies cannot determine whether low blood glucose is the direct cause of an adverse outcome or simply an associated finding.

3. **Using prospective clinical trials to determine whether the benefit of intervention outweighs the short- and long-term risks:** Unfortunately, there are no randomized controlled trials of interventions at differing thresholds.

It must also be recognized that there are differences between capillary and venous whole blood and plasma glucose levels (Level 3b) (in the range of 10% variation, whole blood being lower than plasma [15]). Most of the studies reviewed were performed on whole blood or plasma from capillary sampling. The term ‘blood glucose’ is used throughout this statement to cover all of the aforementioned methods of sampling and processing.

#### WHO IS AT RISK FOR NEONATAL HYPOGLYCEMIA?

Normal blood glucose levels are maintained by gluconeogenesis (16). Neonatal hypoglycemia most commonly occurs in infants with impaired gluconeogenesis (17), brought about by excess insulin production, altered counter-regulatory hormone production or an inadequate substrate supply. Classically these states occur in SGA (weight at less than the 10th percentile) infants (Table 3) (18), large-for-gestational-age (LGA; weight at more than the 90th percentile) infants, IDMs and preterm infants (Level 3/4) (19-22). Some doubt has been raised as to whether LGA infants who are not IDMs are truly at risk (23). There are questions regarding the validity of fetal growth parameters in predicting neonatal hypoglycemia, but they remain the only readily available tool for assessing accelerated and restricted fetal growth (24).

A number of additional maternal and fetal conditions, particularly those associated with perinatal asphyxia, predispose infants to neonatal hypoglycemia (17). In most of these situations, newborn infants are symptomatic and have blood glucose analyses performed as part of their routine care. Rarely, inborn metabolic or endocrine disorders occur, typically without any identifiable risk factors. The investigation and management of these conditions are beyond the scope of this statement (25).

#### WHEN SHOULD AT-RISK INFANTS BE SCREENED?

There is no study that looks specifically at the optimal timing and intervals for glucose screening. Previously maintained by a maternal-fetal flux of substrates, neonatal glucose levels fall during the first hour or two after birth, reaching a natural trough before rising to stable neonatal levels. The

value of screening well babies during this time is limited. Williams (26) compiled a review of neonatal hypoglycemia for the World Health Organization in 1997. He recommended that infants at risk be screened at 4 h to 6 h of age (Level 5 evidence), asserting that no studies demonstrate harm from a few hours of asymptomatic hypoglycemia.

Cohort studies demonstrate that IDMs frequently experience asymptomatic hypoglycemia by 1 h of age, supporting earlier screening in this population (27). Holtrop (22) found that the average times for finding low glucose levels in LGA and SGA infants were 2.9 h (range 0.8 h to 8.5 h) and 6.1 h (range 0.8 h to 34.2 h), respectively. One can infer that hypoglycemia usually occurs in LGA infants and IDMs within 12 h of birth, and screening beyond this period is not required if blood glucose is maintained at 2.6 mmol/L or higher (Level 4). However, preterm and SGA infants may be vulnerable up to 36 h of age and perhaps later, particularly if regular feeds or intravenous infusions are not yet established (28). The inference is that screening of preterm and SGA infants can be discontinued at 36 h of age if feeding is established and blood glucose is maintained at 2.6 mmol/L or higher (Level 4). Based on the assumption that brief periods of asymptomatic hypoglycemia are benign, it is recommended that screening be initiated in at-risk babies at 2 h of age (after an initial feed) and should be continued until the period of risk is considered over (Level 5 evidence: expert opinion).

'Symptomatic infants' should have a blood glucose assessment without delay as part of the workup for diagnostic and therapeutic purposes.

#### HOW SHOULD SCREENING FOR NEONATAL HYPOGLYCEMIA BE PERFORMED?

Traditionally, blood glucose has been conveniently measured on capillary samples using chemical strips or portable, bedside glucose meters as a substitute for formal laboratory analysis. Unfortunately, many of these 'point-of-care' methods are not reliable at the low glucose levels (by adult comparison) found in healthy newborns, and are prone to sample or observer error (29,30) (Level 3b). In addition, variations between capillary and venous blood (31), blood and plasma, and immediate and stored samples may confound results (Level 3b); in particular, delays in processing may result in artefactually lower levels. Given the discomfort, cost and inconvenience of repeated testing for glucose levels, it is clear that fewer, more accurate and more reliable laboratory tests are preferable to a larger number of less reliable 'point-of-care' samples with the associated false positives and negatives (32). It is likely that newer, quicker and more robust 'point-of-care' technologies will improve the quality and ease of screening, as well as provide opportunities for research into the utility and cost effectiveness of screening. Therefore, it is recommended that use of capillary glucose strips and reflectance meters be minimized and, ultimately, replaced by more accurate and reliable methods as they become increasingly available. If 'point-of-care' methods are used, a formal process for assuring quality control at the bedside should be in place and rapid laboratory testing

should be available to verify glucose levels that may require intervention.

#### WHAT LEVELS OF BLOOD GLUCOSE REQUIRE INTERVENTION?

##### Symptomatic hypoglycemia

It has been known for some years that symptomatic hypoglycemia results in neuronal injury (33), making urgent intervention desirable in sick infants. Because there is no absolute level at which intervention is mandated, the proposed cut-off (repeated levels of less than 2.6 mmol/L in an at-risk infant) is recommended.

##### Asymptomatic hypoglycemia

Population data suggest that blood glucose levels as low as 2.0 mmol/L (or even 1.8 mmol/L at 1 h of age) are not uncommon in healthy newborns (Level 2a). In at-risk infants, however, outcome data support raising the intervention threshold. Lucas et al (9) suggest that persistent glucose levels of less than 2.6 mmol/L in preterm infants may have adverse long-term effects (Level 2b). More recently, in 1999, Duvanel et al (34) looked at the neurodevelopmental outcomes in a cohort of 85 SGA preterm infants in relation to episodes of hypoglycemia (defined as a level less than 2.6 mmol/L) (Level 2b). Long-term follow-up of these infants (compared with nonhypoglycemic control subjects) demonstrated an association between hypoglycemia and lower head circumference and developmental scores. Their data suggested increasing the severity of sequelae with increasing duration of hypoglycemia, even when asymptomatic. Steninger et al (35) followed-up 28 IDMs at eight years of age and matched, healthy control subjects and discovered evidence of minimal neurological dysfunction in the whole group, most significant with blood glucose levels of less than 1.5 mmol/L (Level 2b). It is worth noting that most of these babies had asymptomatic hypoglycemia.

Williams (26) supports the cut-off of less than 2.6 mmol/L in at-risk infants at 4 h to 6 h of age. Cornblath et al (36) proposed the concept of operational thresholds, the range of blood glucose concentrations at which clinicians should consider intervention. They distinguished between the threshold glucose value that requires action (2.0 mmol/L) and the target glucose level that interventions are aimed at (2.6 mmol/L or greater) (Level 5).

It seems that, in at-risk infants, blood glucose levels below 2.6 mmol/L, particularly if persistent or repeated, may be associated with adverse outcomes. There is a strong case for randomized clinical trials comparing interventions, intervention thresholds and their long-term outcomes.

The following recommendations are outlined in the attached algorithm (Figure 1).

- Asymptomatic, at-risk babies should receive at least one effective feed before a blood glucose check at 2 h of age and should be encouraged to feed regularly thereafter. At-risk babies who have a blood glucose of less than

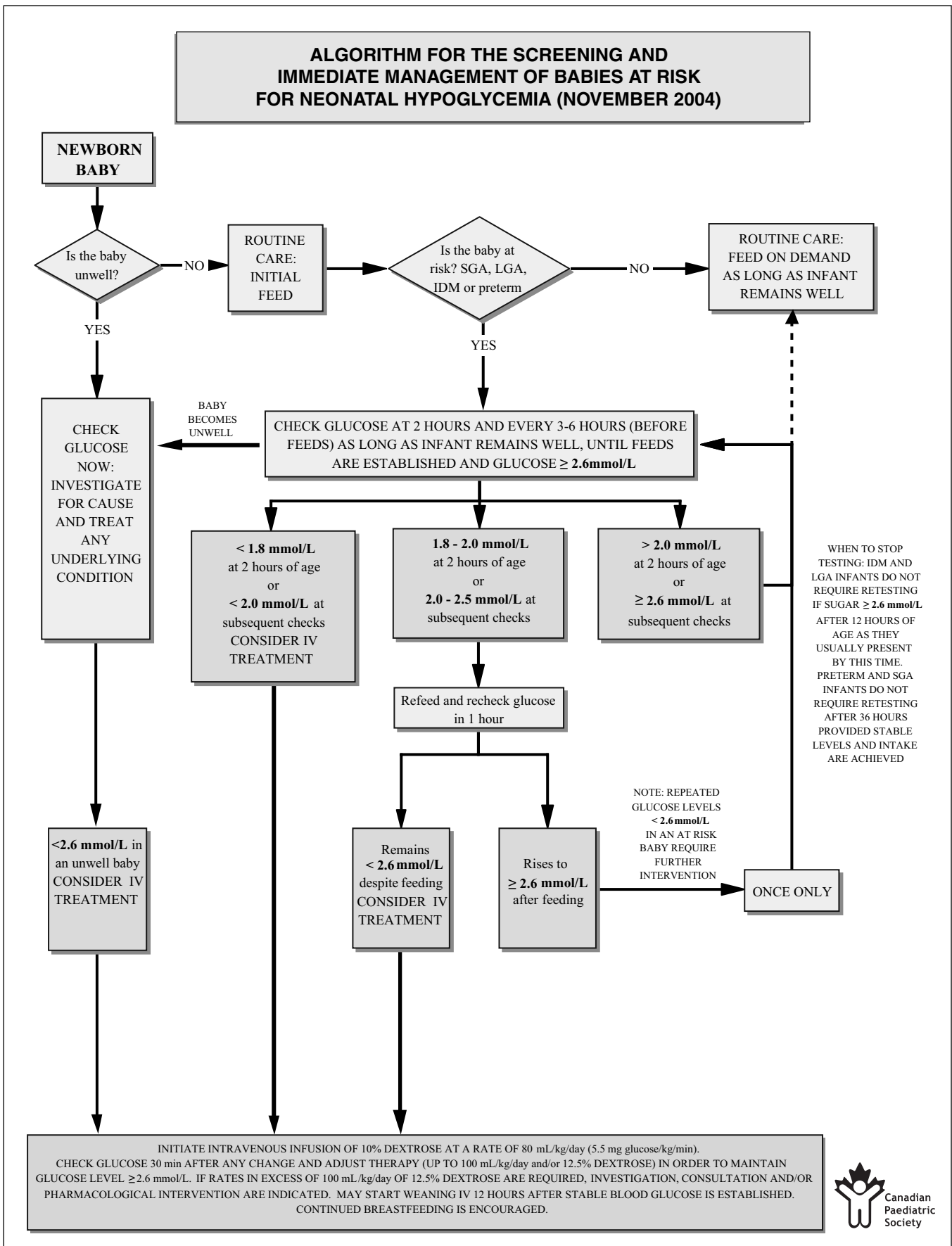


Figure 1) Screening for neonatal hypoglycemia. IDM Infant of diabetic mother; IV Intravenous; LGA Large-for-gestational-age; SGA Small-for-gestational-age

1.8 mmol/L at 2 h of age despite one feed (breastfeed or approximately 5 mL/kg to 10 mL/kg of formula or glucose water), or less than 2.0 mmol/L after subsequent feeding, should receive an intravenous dextrose infusion.

- At-risk babies who repeatedly have blood glucose levels of less than 2.6 mmol/L despite subsequent feeding should also be considered for intravenous therapy.

### WHAT INTERVENTIONS SHOULD BE OFFERED WHEN NEONATAL HYPOGLYCEMIA IS SUSPECTED?

There are, essentially, two approaches. The first supports increased energy intake (orally or intravenously), while the second supports increased mobilization of energy stores (using counter-regulatory hormones, such as glucagon or corticosteroids) (37,38). Pragmatically, the urgency and nature of interventions depend on the presence of symptoms and the severity of the hypoglycemia.

#### Asymptomatic hypoglycemia

Common clinical practices in both the prevention and treatment of asymptomatic hypoglycemia include increased breastfeeding frequency, supplementation with breastmilk or a breastmilk substitute, or intravenous glucose therapy (39). No clinical trials have been performed to demonstrate the benefit of one supplement over another (or, indeed, over breastfeeding on demand [40]) on long-term outcome. Frequent breastfeeding on demand should be encouraged in at-risk babies, and, if formula fed or supplemented, the volume of enteral intake should be adjusted according to the size, age and gestation of the infant (41).

There is some evidence that increased carbohydrate intake prevents low blood glucose levels in healthy term breastfed infants. Martin-Calama et al (42) found in a randomized trial that routine supplementation with dextrose water reduced the likelihood of hypoglycemia. Randomized clinical trials in SGA (43) and appropriate-for-gestational-age (44) infants found that augmented glucose formulas raise blood glucose and prevent hypoglycemia (Level 1b).

When feeding interventions are offered for low blood glucose, levels should be rechecked in 60 min to ensure that there has been a response.

If increased enteral caloric intake is not effective, current practice is to provide intravenous glucose. The initial glucose infusion regime is 80 mL/kg/day of 10% dextrose, providing 5.5 mg/kg/min of glucose, in keeping with studies that have measured glucose flux in newborns (45-48) (Level 3b). Infants with very low glucose levels, particularly those with levels less than 1.8 mmol/L, should be managed with some expedience, confirming response to intervention in a timely fashion (a response to intravenous interventions should occur within 30 min) (49). A single minibolus of 2 mL/kg of 10% dextrose at the start of an infusion more rapidly achieves steady state levels, but the benefit of this practice in asymptomatic babies is uncertain (Level 4). Due to the short

duration of action of glucose, repeated miniboluses without an increase in the infusion rate are not recommended.

#### Symptomatic hypoglycemia

There is both observational evidence and clinical consensus that sick, hypoglycemic infants, particularly those with neurological signs, should be treated immediately with an intravenous infusion of glucose.

The effect of intravenous interventions may be rechecked after 30 min. The target level should be 2.6 mmol/L or higher. An initial failure to respond to intravenous glucose requires a stepwise increase in glucose supply, with a review of blood glucose 30 min after each increment. Changing from 10% to 12.5% dextrose will increase intravenous intake by 25%, as would a rate increase from 80 mL/kg/day to 100 mL/kg/day. An increase from 100 mL/kg/day to 120 mL/kg/day of 12.5% dextrose raises the glucose supply from 8.7 mg/kg/min to 10.4 mg/kg/min. If this infusion rate fails to keep blood glucose levels at 2.6 mmol/L or higher, further investigation, specialist referral and/or pharmacological intervention (eg, intravenous glucagon) should be considered (50-54) (Level 4). Investigations should be aimed at identifying endocrine pathology (particularly hyperinsulinism) and inborn errors of metabolism. Glucagon by intravenous bolus (0.1 mg/kg to 0.3 mg/kg) or infusion (10 µg/kg/h to 20 µg/kg/h) has been observed to raise blood glucose and prevent recurrent episodes of hypoglycemia in both term and preterm infants. Alternative therapies include hydrocortisone, diazoxide and octreotide, but data are limited in their use for the initial management of hypoglycemia.

Breastfeeding may be continued without risk of overhydration because the volume of colostrum is small. To avoid overhydration and hyponatremia in supplemented infants, oral and intravenous intake should not exceed 100 mL/kg/day without careful monitoring for dilutional hyponatremia. Blood glucose levels should be checked frequently until interventions result in stable glucose levels of 2.6 mmol/L or higher; failure to achieve this level requires re-evaluation and consultation. Intravenous dextrose can be weaned when levels have been stable for 12 h.

### HOW FREQUENTLY SHOULD ASYMPTOMATIC, AT-RISK INFANTS BE SCREENED?

Given the paucity of evidence on the adverse effect of glucose levels between 1.8 mmol/L and 2.5 mmol/L in asymptomatic infants over several hours, a staged approach to screening and intervention is suggested. Because feeding raises blood glucose (55) and stimulates ketosis (12), it seems rational to feed at-risk infants at regular intervals, while screening before feeds.

Holtrop (22) showed that IDMs (and, by inference, LGA infants) were most likely to develop hypoglycemia in the first few hours of life – as a consequence, screening is not required in this population after 12 h of age if levels remain at 2.6 mmol/L or greater. SGA and preterm infants may become hypoglycemic as late as the second day (although this may be

prevented by establishing intake). It would be reasonable to screen once or twice on the second day of life, to ensure levels remain at 2.6 mmol/L or higher in this group. If there are no feeding concerns and the infant is well, screening may be discontinued at 36 h of age (Level 2b).

### HOW SHOULD CAREGIVERS BE EDUCATED OR COUNSELLED REGARDING SCREENING FOR NEONATAL HYPOGLYCEMIA?

Both parents and health care providers require education regarding screening. Parents should be aware that their child is symptomatic or at risk, and therefore, requires blood testing at regular intervals. An informed explanation, possibly with the aid of a parent handout ("Checking blood glucose in newborn babies", pages 731-732), will help ensure appropriate parental participation in monitoring and allay fears if further interventions are required. An algorithm (Figure 1) is provided to assist health care providers in the use of this statement.

### SUMMARY

Although blood glucose levels as low as 1.8 mmol/L may be considered normal in healthy babies in the first few hours of life, adverse short- and long-term outcomes may result from levels lower than 2.6 mmol/L in those who are at-risk, particularly if the hypoglycemia is persistent or symptomatic. Screening and intervention is therefore aimed at the detection and treatment of infants who are at risk.

### RECOMMENDATIONS

- Routine screening of appropriate-for-gestational-age infants at term is not recommended (Grade of Recommendation C). It is recommended that IDMs (gestational or otherwise), preterm infants (less than 37 weeks) and SGA infants (weighing at less than the 10th percentile) be routinely screened for neonatal hypoglycemia (Grade of Recommendation C). Until further data are available, LGA infants (weighing at higher than the 90th percentile) should be considered at risk (Grade of Recommendation D).
- Blood glucose screening of asymptomatic, at-risk infants may be performed at 2 h of age and every 3 h to 6 h after this, in keeping with breastfeeding practices. Testing may be discontinued after 12 h in LGA infants and IDMs if blood glucose levels remain at 2.6 mmol/L or higher, and after 36 h in SGA and preterm infants if feeding has been established and blood glucose levels remain at 2.6 mmol/L or higher. Symptomatic and unwell babies require immediate glucose testing (Grade of Recommendation C).
- It is recommended that, where possible, methods should be instituted to measure blood glucose that are quality-controlled, accurate and reliable in the range of 1 mmol/L to 3 mmol/L (Grade of Recommendation D).
- At-risk infants with glucose levels less than 1.8 mmol/L on one occasion (assuming one effective feed), or repeatedly less than 2.6 mmol/L, require intervention (Grade of Recommendation C). Symptomatic infants should be treated immediately for blood glucose levels less than 2.6 mmol/L; there should be concurrent investigation and management of the underlying cause.
- Enteral supplementation may be used in asymptomatic infants with blood glucose levels of 1.8 mmol/L to 2.5 mmol/L to augment caloric intake, rechecking levels in 60 min to identify persistent hypoglycemia (Grade of Recommendation D).
- It is recommended that symptomatic, hypoglycemic infants (and asymptomatic infants who have failed to respond to enteral supplementation) be treated with intravenous dextrose solution. Consider investigation, consultation and pharmacological intervention if target blood glucose levels are not achieved by intravenous dextrose (Grade of Recommendation C).

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.