Screening guidelines for newborns at risk for low blood glucose
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Abstract
Hypoglycemia in the first hours to days after birth remains one of the most common conditions facing practitioners across Canada who care for newborns. This statement addresses a number of areas pertaining to hypoglycemia including the topics; How should screening for neonatal hypoglycemia be performed? How is neonatal hypoglycemia defined? Who is at risk for neonatal hypoglycemia? When should at-risk infants be screened? What levels of blood glucose require intervention? What interventions should be offered when neonatal hypoglycemia is diagnosed? How frequently should asymptomatic, at-risk infants be screened? Additional advice is provided regarding the use of dextrose gels and how to ensure safe discharge of these affected infants to reduce the risk of hypoglycemia recurring after leaving the hospital. This version differentiates the approach to hypoglycemia during the transitional phase in the first 72 hours of life to persistent hypoglycemia that occurs beyond this time point.

Keywords: hypoglycemia, dextrose gel, point of care, newborn

This statement provides an update to the previous version from 2004. Despite the passage of many years the questions remain largely the same. [1]. Compared to the previous versions of this statement, transitional hypoglycemia in the first 72 hours after birth is now explicitly defined as < 2.6 mmol/L. This change allows for an emphasis that persistent hypoglycemia beyond the first 72 hours after birth is defined by levels below <3.3 mmol/L.

An algorithm has been included providing direction in managing infants at risk for neonatal hypoglycemia in the first 72 hours after birth, see Figure 1.
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Management of Hypoglycemia

Baby unwell or symptomatic, or cannot feed:
- Initiate D10W infusion at fluid requirements
- If symptomatic give D10W bolus 2mL/kg over 15 min
- Check blood glucose in 30 min

Well baby who can feed and is at risk of hypoglycemia:
- Glucose < 2.6
  - Give 40% glucose gel 0.5mL/kg, and breastfeed or bottlefeed 5 mL/kg
  - Check glucose 30 min post-feed
  - Tolerating feeds and glucose ≥ 1.8

Glucose ≥ 2.6
- Feed ad lib
- Check glucose prior to next feed

Tolerating feeds and glucose ≥ 1.8
- Glucose < 2.6
  - Give 40% glucose gel 0.5mL/kg, and bottlefeed 5 mL/kg & breastfeed
  - Check glucose 30 min after end of the feed

Glucose ≥ 2.6
- Monitor pre-feed or every 2 to 3h until two consecutive samples ≥ 2.6

Glucose < 2.6
- Target range is 2.6 to 5.0 in < 72h, and 3.3 to 5.0 if ≥ 72h
- Increase D10W infusion every 30 min by 1 mL/kg/h checking glucose after 30 min, until within target range
- Calculate the lowest glucose infusion rate (GIR) at which blood glucose is within target range
- Calculate D9%W concentration needed in order to stay within the maximum tolerated/desired daily fluid intake
- Check electrolytes in 6 to 12 hours

- If GIR is > 8 mg/kg/min, Level 3 Care needed and central access should be considered
- If GIR > 10-12 mg/kg/min, requires medication

- Monitor glucose every 3 h
  - Once glucose > 3.3, introduce enteral feeds as tolerated, and wean IV stepwise
  - Continue glucose monitoring pre-feed until on full enteral feeds and two consecutive samples > 3.3

Glucose ≥ 2.6
- Monitor glucose

1 Babies who are unwell or symptomatic, or cannot feed have the initial glucose checked at the time of first encounter
2 Well babies at risk of hypoglycemia should feed as soon as possible after birth, and have initial glucose check at 2 hours
3 Low glucose threshold is 3.3 after 72 hours of age, and when glucose is actively managed with IV dextrose (all glucose values are in mmol/L)
4 If delay in starting IV in hypoglycemia, give 40% glucose gel 0.5mL/kg
5 Glucose content of 2mL 5%W is same as 0.5mL 40% glucose gel
Search strategy

A MEDLINE search was performed for studies up to March 2017 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. No randomized clinical trials relating to strategies for screening for neonatal hypoglycemia in at-risk infants were identified. All case-control and cohort studies were reviewed. Levels of evidence and grades of recommendations were assigned according to the Oxford Centre for Evidence-Based Medicine guideline [2].

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 low glucose levels, and are prone to sample or user error [3][4] (Level 3b). In addition, variations between capillary and venous blood [5], blood and plasma, and immediate and stored samples may confound results (Level 3b). In particular, delays in processing may result in artefactually lower levels. Capillary and venous whole blood and plasma glucose levels (Level 3b) may differ in the range of 10% variation, with whole blood being lower than plasma [6]. While acute management may be initiated based on bedside point of care capillary whole blood sampling to prevent delay, any diagnosis or “label” of persistent hypoglycemia should be confirmed by laboratory assays of serum samples. It is likely that more accurate ‘point-of-care’ technologies will be developed and improve the quality and ease of screening, as well as provide opportunities for research into the utility and cost effectiveness of screening.

Continuous glucose monitors have looked promising and may prove to be beneficial in monitoring neonates. Barriers to this technology include decreased accuracy at lower glucose levels, delays in the immediacy of the glucose measures, need for ongoing calibration, limited surface area for placement on small neonates for the sensors, and lack of treatment protocols [7][8].

How is neonatal hypoglycemia defined?

It is difficult to define neonatal hypoglycemia by a single value of glucose applicable to all clinical situations and to all infants and this has been the case since glucose levels were first measured in neonates [9]. At least in the 48 – 72 hours after birth, infants may develop signs suggestive of hypoglycemia over a range of blood glucose levels that are substantially lower than normal adult levels. In adults or older children, Whipple’s triad (signs and symptoms of hypoglycemia, low serum glucose level, and the resolution of signs and symptoms with the provision of glucose) can be used, but this is often impractical in the neonate yet the principles should be adhered to if possible. Neonatal signs of hypoglycemia in approximate order of frequency are jitteriness or tremors, 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. Since
other conditions may share these clinical manifestations it is critical to document hypoglycemia and confirm whether they disappear with the administration of sufficient glucose to raise the blood sugar to normal levels [10].

<table>
<thead>
<tr>
<th>Signs and Symptoms of Neonatal Hypoglycemia</th>
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<tbody>
<tr>
<td>jitteriness</td>
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<tr>
<td>tremors</td>
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<tr>
<td>cyanosis</td>
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<tr>
<td>convulsions</td>
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<tr>
<td>apnea</td>
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<tr>
<td>tachypnea</td>
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<tr>
<td>weak or high-pitched cry</td>
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<td>limpness</td>
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<td>lethargy</td>
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<tr>
<td>difficulty in feeding</td>
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<tr>
<td>eye rolling</td>
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<tr>
<td>sweating</td>
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<tr>
<td>pallor</td>
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<tr>
<td>hypothermia</td>
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<tr>
<td>cardiac arrest</td>
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<td>cardiac failure</td>
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</tbody>
</table>

So-called “normal ranges” are presumably dependent on the infant’s size, gestation, the presence of previous hypoglycemia, and the 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 factors.

There are four approaches to defining a safe range for blood glucose, all with limitations. [11][12]

**Using the presence of clinical manifestations**

*Using normative ranges:* Studies of exclusively breastfed, appropriate for gestational age (AGA), term babies, show that blood glucose levels fall immediately after birth from two-thirds of maternal levels to as low as the 5th percentile or approximately 1.8 mmol/L at 1 h of age (Level 2b) [13][14] and subsequently rise to levels > 2.0 mmol/L that is maintained for 72 h [14]. Approximately 12% to 14% of normal, AGA breastfed newborns have a blood glucose level of < 2.6 mmol/L in the first 72 hours after birth [15] after which babies generally maintain a glucose level > 3.3 mmol/L [12]. Preterm infants may take longer to reach this threshold.

*Using the presence or absence of acute normal physiologic metabolic and endocrine changes:* In response to hypoglycemia there are normal physiological responses such as a rise in ketones, growth hormone, cortisol, and catecholamines and the suppression of insulin.

*Using the presence or absence of sequelae:* A number of studies in at-risk term, preterm and small-for-gestational-age (SGA; weight < 10th %tile) infants have suggested an association of blood glucose levels of < 2.6 mmol/L with abnormal short (Level 4) and long-term neurological (Level 2a) or neuroimaging changes (Level 4) [10][16][17]-[19] Other studies have indicated that a lower glucose level within the first 72 hours after birth, is required for long-term sequelae [20] Yet some studies have shown no harm from transient hypoglycemia [21][22] but rather an increased risk of long term sequelae with recurrent episodes of hypoglycemia. [19]
Unfortunately, given the wide range of suggested normal blood glucose levels, the presence of significant comorbidities in the population, and the myriad causes of low blood glucose, cohort and case-control studies cannot determine causation between low blood glucose and adverse outcome. Evidence exploring hypoglycemia outside of the initial transitional period is less abundant. There are suggestions that therapeutic goals for glucose levels in infants with persistent hypoglycemia outside of the transitional period, should be ≥ 3.3 mmol/L. [23][24][25]

**Who is at risk for neonatal hypoglycemia?**

Impairment of gluconeogenesis [26] is the most common cause in infants with hypoglycemia [27]. Specific etiologies include, excess insulin production, altered counter-regulatory hormone production or inadequate substrate supply. Classically these states can occur transiently in small for gestational age infants (weight <10th percentile) (Table 1) [28], large for gestational age (LGA; weight > 90th percentile) infants, infants of diabetic mothers (IDMs) and preterm infants (Level 3/4) [29]-[32]. Questions exist as to whether non-syndromic LGA non-IDM infants are truly at risk although other infants with conditions such as Beckwith-Wiedemann syndrome need to be followed closely [33]. A number of additional maternal and fetal conditions, including maternal use of labetalol or late preterm administration of antenatal steroids [34][35] as well as intrauterine growth restriction and perinatal asphyxia, can also result in hypoglycemia. More rarely, metabolic and endocrine disorders may lead to persistent neonatal hypoglycemia [27] however their disease specific investigations and management are beyond the scope of this statement [36]. Thresholds for treatment may differ depending on the etiology of hypoglycemia. While <2.6 mmol/L has generally been adopted as a threshold for treatment in otherwise healthy infants in the transitional period, those with documented hyperinsulinism may be deserving of a higher target of 3.3 mmol/L. The higher threshold may be warranted due to the absence of alternative fuels in this non-ketotic state. [37]

### Table 1

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

<table>
<thead>
<tr>
<th>Gestation (completed weeks)</th>
<th>Birthweight (g)</th>
<th>10th percentile</th>
<th>90th percentile</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>37</td>
<td>2552</td>
<td>2452</td>
<td>3665</td>
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<tr>
<td>38</td>
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<td>39</td>
<td>2942</td>
<td>2825</td>
<td>4049</td>
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<td>40</td>
<td>3079</td>
<td>2955</td>
<td>4200</td>
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<tr>
<td>41</td>
<td>3179</td>
<td>3051</td>
<td>4328</td>
</tr>
<tr>
<td>42</td>
<td>3233</td>
<td>3114</td>
<td>4433</td>
</tr>
</tbody>
</table>

*Adapted with permission from reference [18]*
When and how frequently should at-risk infants be screened?

No study evaluating the optimal timing and intervals for glucose screening was identified. There is insufficient evidence to support screening asymptomatic infants without risk factors for hypoglycemia.

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 at several hours of age, a staged approach to screening and intervention is suggested. Because feeding raises blood glucose \[38\] and stimulates ketosis \[39\], it seems rational to feed at-risk infants at regular intervals, while screening before feeds.

Holtrop \[32\] showed that IDMs (and, by inference, LGA infants) were most likely to develop hypoglycemia in the first few hours after birth. 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). If there are no feeding concerns and the infant is well, screening may be discontinued at 24 h of age (Level 2b). It would be reasonable to screen once or twice on the second day after birth, if there have been more than one glucose reading below 2.6 mmol/L in the first 24 hours to ensure levels remain at or above this level after this period.

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

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”), 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.

What levels of blood glucose require intervention?

First 72 hours

Symptomatic hypoglycemia

Symptomatic hypoglycemia results in neuronal injury \[40\], making urgent intervention desirable in sick infants. Based on the available data, maintaining glucose levels \(\geq 2.6\) 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 [41] suggest that persistent glucose levels of < 2.6 mmol/L in preterm infants may have adverse long-term effects (Level 2b). More recently, Duvanel et al [42] studied neurodevelopmental outcomes in a cohort of 85 SGA preterm infants in relation to episodes of hypoglycemia (defined as < 2.6 mmol/L) (Level 2b). Compared to non-hypoglycemic control subjects, 6 or more episodes of hypoglycemia was associated with lower head circumference at 12 and 18 months as well as at 5 years of age. Furthermore, psychometric testing using the McCarthy’s test at 3.5 years of age demonstrated impairments compared to controls without exposure to neonatal hypoglycemia. It must be noted that 58% of this cohort had severe hypoglycemia between 0.6 to 1.6 mmol/l so it is uncertain whether these results would be reflective in a modern cohort of more aggressive management of glucose.

Stenninger et al [43] followed-up 28 IDMs (13 with hypoglycemia <1.5 mmol/L and 15 without) at eight years of age and matched, healthy control subjects and discovered minimal evidence of neurological dysfunction whether hypoglycemic or not using the Griffith’s developmental and Movement ABC tests (Level 2b). It is worth noting that most of these babies had asymptomatic hypoglycemia.

Williams [44] supports the cut-off of < 2.6 mmol/ L in at-risk infants at 4 h to 6 h of age. Cornblath et al [24] 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). Recently, the 4.5 year follow up of a large cohort by McKinlay et al [19] indicated an increased risk in some measures of neurological impairment, such as executive functioning and visual motor function, with recurrent (3 or more episodes <2.6 mmol/L) or severe (<2 0 mmol/L) hypoglycemia.

It seems that, in at-risk infants, blood glucose levels < 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.

Recommendations for management of hypoglycemia are outlined in the algorithm, see Figure 1.

Beyond 72 hours:

Recent guidelines have suggested a raised threshold and/or treatment goal for infants beyond the transitional period, defined as 48 hours by some or 3 days after birth by others [23][25]. Much of the evidence to recommend such levels is based on the follow up of children with hyperinsulinism, a major cause of persistent hypoglycemia, who are at increased risk of neurological sequelae due to lack of alternate fuel source of ketones for the brain. Additional motivating factors include the development of neuroglycopenic and neuroendocrine responses in adults and older children at glucose levels as low as 2.7-2.8 mmol/L [45][46].
While glucose values increase perhaps very slightly with age, normal glucose ranges do not differ much in children versus adults. For example, one study showed that the mean glucose in children after a prolonged 24 hour fast was 3.6 (2.7 - 4.5) mmol/L in children 1-12 months old, 3.3 mmol/L (2.8-3.8) in children 1-7 years old, and 3.8 mmol/L (3.0-4.3) in children 7-15 years old. [47][48]

Although difficult to define hypoglycemia by a specific cut off, taking into account safety, limiting morbidity, and over investigation and treatment, after the transitional period, a laboratory confirmed glucose value of ≤ 3.3 mmol/L should be defined as persistent hypoglycemia warranting further assessment. Those requiring ongoing treatment for persistent hypoglycemia should have therapeutic targets of ≥ 3.3 mmol/L, above the cut off for neurogenic and neuroglycopenic symptoms. A critical sample to aid in the diagnosis of an underlying etiology for persistent hypoglycemia at ≥ 72 hours should be collected when a point of care glucose is < 2.8 mmol/L. The distinction between the two values for investigation and therapeutic target reflects the need to ensure the potential normally expected biochemical physiological responses needed to make a diagnosis of etiology. As by the point of a glucose level <2.8 mmol/L one should normally see a suppressed insulin, elevated ketones, and increased counter regulatory hormones (GH, cortisol). In addition, there is a possible 20 % error in measurement that may exist between point of care and laboratory glucose values. Given the volume of blood required for a critical sample it seems prudent to restrict collection of such bloodwork to situations in which the point of care sample has a reading of < 2.8 mmol/L to try and ensure a useful critical sample. This will avoid the situation of being unable to interpret the critical sample results when the laboratory glucose is ≥ 3.3 mmol/L. The thresholds for defining hypoglycemia and when to obtain critical samples are provided in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Thresholds For Investigation and Treatment of Hypoglycemia</th>
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<tbody>
<tr>
<td><strong>Therapeutic goal</strong></td>
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<td></td>
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<tr>
<td><strong>Confirmatory lab glucose</strong></td>
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</table>

* Critical sample should be sent to determine etiology in addition to lab glucose. Critical samples may be sent earlier than this time point if strong suspicion of an endocrine or metabolic etiology.

Neonates being monitored for persistent hypoglycemia should have a 5 to 6 hours fast prior to discharge to ensure their safety at home if time between feeds is prolonged. Additionally, the underlying diagnosis should be ascertained and specific medical management (eg. Diazoxide in hyperinsulinism) initiated in hospital with parental education completed with respect to recommended frequency of feeding., home blood glucose monitoring, medication delivery as applicable, and treatment of hypoglycemia.

Our recommendations are similar to those in the recent PES recommendations [25]. While the PES statement used a cutoff of 48 hours, the transition point likely lies somewhere between 48-72 hours. Due to concerns over increased admission rates for hypoglycemia and given the uncertainty around the 48-hour time point we believe 72 hours allows a balance between safety and minimizing negative impacts to families and care providers. Importantly a distinction between the transition period and the period beyond...
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is recognized with a high index of suspicion for investigations and intervention suggested after 72 hours of life for hypoglycemia that persists below suggested levels.

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) [49][50]. Pragmatically, the urgency and nature of interventions depend on the presence of symptoms and the severity of the hypoglycemia. Additional treatment is disease specific, for example diazoxide or octreotide in hyperinsulinemia and recombinant growth hormone in growth hormone deficiency.

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, intrabuccal dextrose gel, or intravenous glucose therapy [51][52]. No clinical trials have been performed to demonstrate the benefit of one supplement over another (or, indeed, over breastfeeding on demand [53]) 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 [54]. Additionally, delaying the first bath has also been found to reduce incidence of hypoglycemia and this practice may help avoid additional cases. [55]

There is some evidence that increased carbohydrate intake prevents low blood glucose levels in healthy term breastfed infants. Randomized clinical trials in SGA [56] and AGA [57] 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 30 min to ensure that there has been a response.

If increased enteral caloric intake is not effective, historically the next intervention would be to provide intravenous glucose. More recently dextrose gels have gained traction in the management of hypoglycemia and are discussed in the next section. When using an IV route however, the recommended 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 [58]-[61] (Level 3b). Infants with very low glucose levels, particularly those with levels < 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) [62]. A single bolus 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, after one or two boluses of dextrose the infusion rate or concentration of dextrose should be increased.
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. 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. The effect of changes in the glucose infusion rate (GIR) from either increasing the total fluid intake (TFI) and/or concentration are shown in Figure 2 below and online calculators exist to aid the practitioner in determining the effects of changes to either dextrose concentration or infusion rates.

[63]

**Figure 2**

<table>
<thead>
<tr>
<th>TFI: ml/kg/day (ml/kg/h)</th>
<th>GIR: mg / kg / min</th>
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<td>D 5</td>
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<tr>
<td>60 (2.5)</td>
<td>2</td>
</tr>
<tr>
<td>80 (3.3)</td>
<td>2.8</td>
</tr>
<tr>
<td>100 (4.1)</td>
<td>3.4</td>
</tr>
<tr>
<td>120 (5.0)</td>
<td>4.2</td>
</tr>
<tr>
<td>140 (5.8)</td>
<td>4.8</td>
</tr>
<tr>
<td>160 (6.6)</td>
<td>5.5</td>
</tr>
<tr>
<td>180 (7.5)</td>
<td>6.3</td>
</tr>
<tr>
<td>200 (8.3)</td>
<td>6.9</td>
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With respect to venous access, previous recommendations of placing a central venous line for concentrations ≥15% may not be necessary. Recent evidence has emerged supporting the integrity of peripheral veins using dextrose concentrations as high as 20%. No difference in rate of IV loss was noted in patients randomized to receive dextrose solutions at these higher dextrose concentrations. [64]

If infusions fail to keep blood glucose levels at appropriate levels, or high rates (>10 mg/kg/min) are required, further investigation, specialist referral and/or pharmacological intervention (eg, intravenous glucagon) should be considered [65]-[69] (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 30 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 in the transitional period because the volume of colostrum is small. To avoid overhydration and hyponatremia in supplemented infants, oral
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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 and failure to achieve this level requires re-evaluation and consultation. Intravenous dextrose can be weaned when levels have been stable for 12 h.

Dextrose gel

Recently, intrabuccal 0.5 mL/kg of 40% dextrose gel has become available for management of hypoglycemia. [52] This amount of dextrose gel provides 200 mg/kg of glucose equivalent to an intravenous bolus of 2 mL/kg of D10W solution. The Sugar Babies trial [70] compared administration of dextrose gel versus placebo for treatment of hypoglycemia, with the primary outcome being achievement of blood glucose above 2.6 mmol/l after up to two doses. Dextrose gel reduced the frequency of treatment failure compared with placebo (14% vs 24%; relative risk 0.57, 95% CI 0.33–0.98; p=0.04). Additional important outcomes were reduction in admission to NICU for hypoglycemia 14% vs 25%; RR 0.54 (CI 0.31–0.93; p=0.03) and a greater number of babies receiving no supplementation with formula (7% vs 10%; p=0.04).

Outcomes

The cohort from the Sugar Babies trial and a second trial of 102 patients who received dextrose gel with admission to NICU for monitoring with amplitude integrated EEG were evaluated together at 2 years of age. [22] In both, the goal was to maintain blood glucose ≥ 2.6 mmol/L. For the Sugar Babies cohort alone, no difference in developmental outcomes were noted between control and dextrose gel groups. Of concern though, was the finding of sixty-six children (36%) with neurosensory impairment overall for all patients enrolled (1 severe, 6 moderate, 59 mild) with similar rates in both groups (dextrose 38% vs placebo 34%, relative risk 1.11, 95% CI 0.75–1.63). When combined with the patients from the smaller trial and the Sugar Babies group, again no difference in neurosensory impairment was found (risk ratio, 0.95; 95% confidence interval (CI), 0.75 to 1.20; P = 0.67).

The reasons for such a high rate of neurosensory impairment overall are unclear. Whether it is the underlying conditions leading to hypoglycemia or the detrimental effect of hypoglycemia itself is unknown. Supporting the former, is previous work showing that late preterms and those with intrauterine growth restriction have independent risk for neurosensory impairment even with normoglycemia. [71]. Finally, an interesting finding was that infants who tended to spend more time with blood glucose levels > 4.0 mmol/L in the first 48 hours had worse neurodevelopmental outcome. While this did not reach statistical significance, it raises the question of whether overcorrection of low blood glucose may itself lead to harm.

Investigations for causes of persistent hypoglycemia:

Generally, infants with hypoglycemia in the first 72 hours after birth do not require investigations unless there is a strong clinical suspicion at that time of the neonate having a persistent hypoglycemic disorder, such as recurrent severe hypoglycemia. Infants with hypoglycemia that persists beyond this transitional
period, should be evaluated further for possible etiologies. If possible, with the presence of hypoglycemia (glucose < 2.8 mmol/l) a critical sample should be obtained including a confirmatory plasma glucose, beta-hydroxy-butyrate, bicarbonate, lactate, free fatty acids, insulin, growth hormone, cortisol and carnitine. Further workup for possible etiologies should be done with collaboration with specialists in endocrinology, and/or inborn errors of metabolism.

Summary

Although transient blood glucose levels as low as 1.8 mmol/L may be considered normal in healthy babies in the first few hours after birth, 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. Higher thresholds of 2.8 mmol/L for triggering investigations and 3.3 mmol/L for therapeutic targets are recommended after the initial transitional period that occurs in the first few days after birth. Screening and intervention is therefore aimed at the detection and treatment of infants who are at risk.

Recommendations

- Routine screening of AGA infants at term is not recommended (Grade of Recommendation C). It is recommended that IDMs (gestational or otherwise), preterm infants (< 37 weeks) and SGA infants (weight < 10th %tile) be routinely screened for neonatal hypoglycemia (Grade of Recommendation C). Until further data are available, LGA infants (weight > 90th %tile) 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 ≥ 2.6 mmol/L, and after 24 h in SGA and preterm infants if feeding has been established and blood glucose levels remain at ≥ 2.6 mmol/L. Symptomatic and unwell babies require immediate glucose testing (Grade of Recommendation C).
- It is recommended that, 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 in the first 72 hours after birth with glucose levels < 1.8 mmol/L on one occasion (assuming one effective feed), or repeatedly < 2.6 mmol/L, require intervention (Grade of Recommendation C). Symptomatic infants should be treated immediately for blood glucose levels < 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 30 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).
Dextrose gel may be used as an alternative to intravenous therapy in asymptomatic infants with a blood glucose < 2.6 mmol/L in addition to enteral supplementation. In symptomatic infants, dextrose gel may also be used as a temporizing measure to raise blood glucose while awaiting the establishment of an intravenous dextrose bolus and infusion (Grade of Recommendation B).

Infants with hypoglycemia persisting beyond the first 72 hours should be investigated further if glucose levels ≤ 2.8 mmol/L. A critical sample should be collected in the presence of hypoglycemia.

Infants with persistent hypoglycemia beyond the initial 72 hours after birth should have therapeutic glucose targets of > 3.3 mmol/L.

Infants with persistent hypoglycemia beyond the initial 72 hours after birth should have a 5-6 hour fast with maintenance of glucose ≥ 3.3 mmol/L prior to discharge to ensure safety at home.

References

2. Oxford Centre for Evidence-Based Medicine. Levels of evidence and grades of recommendation.
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