Case Based Learning  St. Joseph Hospital  Level 2 Nursery

NEONATAL HYPOGLYCEMIA

Objectives:

Medical Expert:

1) To review the causes of hypoglycemia in newborns
2) To understand the rationale of Hypoglycemia Protocol used in the L2N (available in the Green Book)

Communicator:

1) To learn how to counsel parents regarding hypoglycemia causes, treatment and prognosis

Resources:


2) Screening guidelines for newborns at risk for low blood glucose. CPS Position Statement; Paediatr Child Health Vol 9 No 10 December 2004

3) Win Tin et al. 15-Year Follow-Up of Recurrent 'Hypoglycemia' in Preterm Infants. Pediatrics 2012;130;e1497

Case:

You are called from 3OBs for a consult on a 4 hour old baby boy with a glucose of 1.9. The baby was born to 32 y.o. G2 A1 previously healthy mom. Mom’s serology was protective and she is GBS negative. Her blood group is O+ve. Glucose tolerance test at 28 weeks was normal. Pregnancy was complicated by mild PIH in the last 3 weeks and mom has been on labetalol with good BP response. She went into spontaneous labour at 38 weeks and 6/7 gestation and infant was delivered via C/S for failure to progress. His Apgars were 9 and 9 and he has been well since birth, except for mild jitteriness. His birth weight is 4.35 kg. He was put on breast within the first hour.

Discussion:

1) What risks does this infant have for postnatal hypoglycemia?
2) Is there anything else you want to know on history and physical exam?
3) What is your list of possible differentials?
Infant was fed 30 mls of formula and a repeat blood glucose is pending. He remains jittery but well otherwise. He does not have any dysmorphic features. His respiratory, cardiovascular and abdominal exams are normal. He has normal male genitalia, normal tone and skin exam. You confirm with mom and the obstetrical team that the OGTT was indeed normal, and that mom was not on any other medications that would cause jitteriness.

Discussion:

1) Review the Hypoglycemia protocol in your Green Book. What is the right treatment plan at this point?
15-Year Follow-Up of Recurrent "Hypoglycemia" in Preterm Infants
Win Tin, Greta Brunskill, Tom Kelly and Susan Fritz

*Pediatrics* 2012;130;e1497; originally published online November 5, 2012;
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The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://pediatrics.aappublications.org/content/130/6/e1497.full.html
15-Year Follow-Up of Recurrent “Hypoglycemia” in Preterm Infants

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**KEY WORDS**
hypoglycemia, preterm, developmental disabilities

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**WHAT’S KNOWN ON THIS SUBJECT:** It has been widely thought for the past 20 years that recurrent low blood glucose levels ≤2.5 mmol/L (45 mg/dL), even in the absence of any suggestive clinical signs, can harm a preterm infant’s long-term development.

**WHAT THIS STUDY ADDS:** This prospective study showed the outcome at 2 and 15 years later for the preterm infants who had a blood glucose level this low in the first 10 days of life did not differ from that of matched controls.

**BACKGROUND:** Observational study of 543 infants who weighed <1850 g, published in 1988 reported seriously impaired motor and cognitive development at 18 months in those with recurrent, asymptomatic hypoglycemia (plasma glucose level ≤2.5 mmol/L on ≥3 days). No study has yet replicated this observation.

**AIM:** To quantify disability in a similar cohort of children followed up throughout childhood.

**POPULATION:** All children born at <32 weeks’ gestation in the north of England in 1990–1991 and had laboratory blood glucose levels measured daily for the first 10 days of life.

**RESULTS:** Forty-seven index children of the 566 who survived to 2 years had a blood glucose level of ≤2.5 mmol/L on ≥3 days. All of these children and hypoglycemia-free controls, matched for hospital of care, gestation, and birth weight, were assessed at age 2. No differences in developmental progress or physical disability were detected. The families were seen again when the children were 15 years old, and 38 of the index children (81%) and matched controls agreed to detailed psychometric assessment. Findings in the 2 groups were nearly identical (mean full-scale IQ: 80.7 vs 81.2). Findings in the 21 children with a level of ≤2.5 mmol/L on ≥4 days, 7 children with a level this low on 5 days, and 11 children with a level of <2.0 mmol/L on 3 different days did not alter these conclusions.

**CONCLUSIONS:** This study found no evidence to support the belief that recurrent low blood glucose levels (≤2.5 mmol/L) in the first 10 days of life usually pose a hazard to preterm infants. *Pediatrics* 2012;130:e1497–e1503
An important and very influential article by Lucas et al1 published in 1988 opened by commenting that “There has been considerable debate over what should be chosen as a safe lower limit for blood glucose concentration in the neonatal period.” This article provided data on 661 infants who weighed <1850 g at birth, and the authors concluded that “contrary to general belief, moderate hypoglycaemia may have serious neurodevelopmental consequences, and reappraisal of current management is urgently required.”

The authors had used statistical strategies to analyze the data to see if they could find some “threshold” value that reliably predicted an adverse outcome before concluding that glucose concentration of ≤2.5 mmol/L (45 mg/dL) offered the greatest predictive power. They reported that “The number of days on which moderate hypoglycaemia occurred was strongly related to reduced mental and motor development at 18 months corrected age, even after adjustment for a wide range of factors known to influence development.” Similar but less dramatic differences were found when the children were seen again, as part of a larger study2 when the children were 7 to 8 years old.5

These findings have profoundly influenced the neonatal care of the preterm infant across the developed world ever since, while accepting that symptomatic hypoglycemia can cause lasting damage, many have doubted whether low levels are ever damaging when there are no associated clinical signs.4–12 In their systematic review of all the available data in 2006, Boluyt et at10 concluded that none of the 18 eligible studies they identified “provided a valid estimate of the effect of neonatal hypoglycaemia on neurodevelopment.”

Mindful of the need to confirm the findings of the study by Lucas et al,1 clinicians in the north of England initiated an observational study in 1990 designed, among other things, to replicate the earlier study. This article reports the outcome of that study now that it has been possible to assess the outcome for all but 2 of the teenage survivors.

METHODS

Patients
Every infant born before 32 weeks’ gestation in 1990 and 1991 to a mother residing in the north of England was recruited into this prospective study of the child’s neonatal care and later development,13 and most also were recruited into 2 controlled trials13–15 “nested” into this study.

Ethics Approval
Approval for the study was obtained from all 16 district research ethics committees in 1989. The strategy for contacting these families and for reassessing the children when they were 15 years old also was approved by the Newcastle and North Tyneside Health Authority research ethics committee in 2005.

Documentation of Early Care
Details of the early care given to these infants were collected prospectively, and every infant had a blood sample taken each morning at a fixed time in the first 10 days of life. Information on the blood glucose level (glucose oxidase assay) at this time was collected prospectively, and the results of additional glucose samples taken at other times for any clinical reason also were recorded.

Assessment at 2 Years
By using a combination of menstrual history cross-validated by early obstetric ultrasound assessment,16 a total of 781 infants were assessed as having been born before 32 weeks in 1990–1991. All 566 who were still alive were then seen for development assessment at 2 years’ corrected age17 by using the Griffiths scales for Mental Development by a single clinician.18 Forty-eight of the 566 children who had blood glucose levels of ≤2.5 mmol/L at the standard pre-set time for blood sample collection on ≥3 days during the first 10 days of life were identified as index children. Results from 1 child with severe myotonic dystrophy were excluded from analysis, but the findings from all the other children were individually matched with those found in control children who had never had a documented blood glucose level this low, prespecified or not. These controls were chosen from the same birth cohort and matched, first for the hospital of early care, then for gestation at birth, and then for birth weight. No differences in developmental progress or in physical disability were detected,19,20 but because a child’s cognitive and academic potential cannot be assessed reliably this early, it was agreed with the parents that all children would be assessed again as teenagers.

Assessment at 15 Years
All but 2 of 47 families with index children and the families of 47 control children were traced and seen again once the child was at least 15 years old by a research psychologist (GB) who was unaware whether she was in contact with an index or a control family. Information concerning current health and school progress was collected. Thirty-eight of the index children and an equal number of control children also agreed to have a formal psychometric assessment. All of these children had their full-scale IQ determined by using the Short Weschler-III assessment tool,21,22 and nearly all also had their reading and
mathematical ability assessed (by using the relevant Weschler Scales), their behavioral and emotional status assessed (by using the Achenbach Child Behavior Check List), and their adaptation to daily living assessed (by using the Vineland Adaptive Behavior Scale).

RESULTS

Table 1 shows how well matched the psychometrically assessed 38 index and control children had been at birth and during the neonatal period, except in terms of their routinely timed blood glucose measurements. Table 2 summarizes the outcome of their assessment when they were 15 to 16 years old, and Fig 1 shows how very variable the individual IQ values were. The Achenbach scores are reassuring (a normal score is 50 ± 10), whereas the low mean IQ score (85.3) for the 63 fully assessed children without sensorimotor disability (Fig 1) is not unexpected; similar low values have been seen in other long-term cohort studies of infants weighing <1.5 kg at birth.

The 2 children whose outcome is not known at 15 years of age had been entirely healthy and making normal developmental progress when formally assessed at 2 years.

An identical analysis, limited to the 21 infants with a blood glucose level this low at the pre-set time on at least 4 days and the 7 children with a level this low on 5 days, did not alter these conclusions. Neither did an analysis using all the blood glucose samples collected during the first 10 days of life, or an analysis limited to the 11 matched pairs in which the index child had had a level of <2.0 mmol/L on at least 3 different days. In children free from sensorimotor disability, there was no trend for IQ to be lower in children with a low blood glucose level on many different days. Neither is there anything to suggest, from what is known about school performance, that a full psychometric assessment of the remaining 9 index children would have changed these findings.

Factors Making Low Blood Glucose Levels More Likely

Infants recruited into this study received their early care in 13 different units in the north of England, where policies for early fluid management and calorie intake varied widely. Low blood glucose levels were most common on the second to sixth day of life, were rare in infants >9 days old, and were seen least often in units that aimed to give all infants at least 120 mL/kg of 10% dextrose per day intravenously (8.3 mg/kg/min of glucose) once they were 2 days old.

Clinical Signs

Two index children were reported to have had seizures in the first week of life and to have been treated with an anticonvulsant. In neither was the timing of the seizures related to any of the periods when the blood glucose level was low. Neither child ever had a recognizable cerebral ultrasound abnormality, and both had normal IQ scores at follow-up. No other child had any manifestation typically associated with hypoglycemia, such as tremor or stupor, but it has to be accepted that these signs could have been missed in the 20 children who were being ventilated at a time when the blood glucose level was later found to have been low.

Cerebral Palsy and Its Antecedents

Six index and 4 control children had cerebral palsy (Table 2), and all but 2 had an IQ score of <70 (Fig 1). Eight of these 10 children (4 index children and 4 controls) had cerebral palsy had had late (~6 week) cerebral ultrasound scans, all showing major abnormalities. Four children with cerebral palsy also had epilepsy (Table 2).

Self-sufficiency

What is going to matter to these teenagers is not so much whether they have some physical or intellectual disability, but the extent to which it seems likely to impact on their ability to care for themselves, an issue the Vineland Adaptive Behavior Score tries to address (Table 2). Six index and 8 control children had a Vineland score of <60. A combination of cerebral palsy and cognitive problems probably accounted for the low score in 4 index children, and cognitive problems accounted for the low score in the other 2 children.

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**TABLE 1** Characteristics at Birth and Experiences Before Discharge in the 38 Children Who Had a Blood Glucose Level of ≤2.5 mmol/L at a Pre-Set Time on at Least 3 of the First 10 d of Life

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Index Child</th>
<th>Control Child</th>
<th>Mean Paired Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation, d, mean ± SD</td>
<td>207 ± 13</td>
<td>205 ± 15</td>
<td>+2.6 (0.6 to 4.6)</td>
</tr>
<tr>
<td>Birth wt. g, mean ± SD</td>
<td>1330 ± 293</td>
<td>1287 ± 434</td>
<td>+63 (−71 to 196)</td>
</tr>
<tr>
<td>Birth wt. below the 10th percentile, n (%)</td>
<td>8 (21)</td>
<td>4 (10.5)</td>
<td>—</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>21 (55)</td>
<td>24 (63)</td>
<td>—</td>
</tr>
<tr>
<td>Twin or triplet pregnancy, n (%)</td>
<td>6 (16)</td>
<td>8 (21)</td>
<td>—</td>
</tr>
<tr>
<td>Offered ventilator support, n (%)</td>
<td>22 (58)</td>
<td>19 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Days’ support if ventilated, mean</td>
<td>24.8</td>
<td>17.5</td>
<td>+7.3 (−1.9 to 16.5)</td>
</tr>
<tr>
<td>Proven sepsis, n (%)</td>
<td>8 (21)</td>
<td>6 (18)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery for retinopathy of prematurity, n (%)</td>
<td>4 (10.5)</td>
<td>2 (5.3)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery for necrotizing enterocolitis, n (%)</td>
<td>1 (2.6%)</td>
<td>1 (2.5%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Table includes children for whom a full psychometric assessment was possible 15 years later and in their matched controls (who never had a documented low level).

Controls who never had a blood glucose level of ≤2.5 mmol/L were matched, first for the unit where the index child received care in the first 2 wk of life, then for gestation, and then for birth wt.

Paired t test was used to compare the 2 groups.
Cognitive problems seemed to account for the low score in 5 of 8 control children, and 2 of the other 3 children with a low score had had serious behavior problems.

**Outcome in Which Levels Were <2.0 mmol/L**

Eighteen of the 47 index children were found to have had whole blood glucose levels of <2.0 mmol/L on at least 3 separate days in the first 10 days of life. Full assessment was possible in 14 children, and progress is known to have been within normal limits in the other 4 children. The mean (SD) IQ in the 14 who were fully assessed was 81.6 (20.1), and in the matched controls it was 82.2 (20.7). Excluding the 3 index and 3 control children with sensorimotor disability, the results were 88.9 (14.5) and 87.9 (18.9).

**DISCUSSION**

The study by Lucas et al in 1988\(^1\) from Cambridge still remains, according to the authors of the systematic review published in 2006,\(^8\) the only high-quality study to document the subsequent developmental progress of preterm infants known to have been "hypoglycemic" in the neonatal period, although another study by Duvanel et al in 1999,\(^9\) in small-for-gestational-age preterm infants, showed similar findings. The only other high-quality study currently available, according to the authors of this review, was a study that focused on the later progress made by 75 full-term, large-for-date infants who had transient hypoglycemia on the first day of life, and this study found that the later progress of index and control children was virtually identical 4 years later.\(^3\) All of which, not surprisingly, led the authors of that review to conclude that "recommendations for clinical practice cannot be based on evidence because of a lack of valid empirical research." We have known, for 50 years, that a low blood glucose level can cause neonatal seizures,\(^1\) and for 40 years, that it can also cause permanent brain damage.\(^2\) Recent neuroradiologic studies also have started to improve our understanding of how variable this damage may well be,\(^11,33,34\) but we still do not know whether low levels unassociated with any clinical signs can be damaging, particularly in the preterm infant who may not display the same immediate behavioral response to neuronal injury as the term infant.

The current study was a close replication of the study from Cambridge. It used gestation rather than birth weight for eligibility but collected a non-selective cohort of infants of similar size. Both studies only made use of laboratory estimates by using a glucose oxidase method; however, the present Northern study only used laboratory samples taken at a pre-set time once a day for its primary analysis, rather than samples taken whenever the clinician judged appropriate. This method avoided the possibility that more samples might be available for analysis in infants who seemed ill and more immature and might be at risk for a suboptimal outcome for other reasons, a potential weakness in the design of the Cambridge study that the authors acknowledged at the time. Blood sample collection continued for as long as seemed clinically justified in the Cambridge study, but routine sample collection stopped after 10 days in the current study.

Ninety-two percent of the surviving infants in the Cambridge study were reassessed when 18 months old, and all the infants in the Northern study were seen when they were 24 months old. Most of the children in the Cambridge study were seen again when they were 7 to 8 years old, by which time their general IQ scores did not seem to differ, although the scores for reading and arithmetic using the British Ability Scales\(^3\) did still differ.\(^4\) In the Northern study, some information was available

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**TABLE 2**

Outcome at 2 y in All 47 Children Who Were Found to Have Had a Blood Glucose Level of ≤2.5 mmol/L at a Pre-set Time on at Least 3 of the First 10 d of Life and in the 38 for Whom a Full Psychometric Assessment Was Possible 15 y Later and in Their Matched Controls (Who Never Had a Documented Low Level)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Index</th>
<th>Control</th>
<th>Mean Paired Difference (SSS Confidence Interval)</th>
<th>No. of Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious sensorimotor disability at age 2, n (%)</td>
<td>7 (14.9)</td>
<td>6 (12.8)</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>6 (12.8)</td>
<td>4 (8.5)</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>Visually disabled</td>
<td>2 (4.2)</td>
<td>2 (4.2)</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>Uses hearing aids</td>
<td>1 (2.1)</td>
<td>1 (2.1)</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>Special educational provision at 10–15 y, n (%)</td>
<td>3 (6.5)</td>
<td>2 (4.3)</td>
<td>—</td>
<td>46</td>
</tr>
<tr>
<td>Attended a special school</td>
<td>4 (8.7)</td>
<td>4 (8.7)</td>
<td>—</td>
<td>46</td>
</tr>
<tr>
<td>Medication when 10–15 y old, n (%)</td>
<td>5 (11.4)</td>
<td>5 (11.4)</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>On medication for asthma</td>
<td>2 (4.5)</td>
<td>2 (4.5)</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>Treated for severe behavior problems</td>
<td>2 (4.4)</td>
<td>4 (8.9)</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>Full psychometric assessment when ≥15 years old, mean ± SD</td>
<td>80.7 ± 19.8</td>
<td>81.2 ± 15.2</td>
<td>−0.6 (−8.3 to 7.2)</td>
<td>38</td>
</tr>
<tr>
<td>Full-scale IQ (short Wechsler-III)</td>
<td>91.1 ± 18.3</td>
<td>90.2 ± 15.9</td>
<td>+0.9 (−7.5 to 9.2)</td>
<td>36</td>
</tr>
<tr>
<td>Reading (Wechsler WORD score)</td>
<td>84.8 ± 21.4</td>
<td>85.9 ± 17.4</td>
<td>+0.9 (−7.5 to 9.4)</td>
<td>35</td>
</tr>
<tr>
<td>Numeracy (Wechsler WOND score)</td>
<td>51.0 ± 10.2</td>
<td>54.4 ± 13.8</td>
<td>−3.2 (−9.3 to 2.9)</td>
<td>37</td>
</tr>
<tr>
<td>Behavior (total Achenbach score)</td>
<td>74.4 ± 19.1</td>
<td>68.5 ± 16.7</td>
<td>+5.9 (−2.8 to 14.7)</td>
<td>37</td>
</tr>
</tbody>
</table>

\(^a\) Controls who never had a blood glucose level of ≤2.5 mmol/L were matched, first for the unit where the index child received care in the first 2 wk of life, then for gestation, and then for birth wt.

\(^b\) Paired \(t\) test was used to compare the 2 groups.
on all but 1 of the index children when they were 15 years old, the incidence of disability in the 2 groups was still almost identical, and there was no difference in IQ in the 38 pairs who agreed to full psychometric assessment, and in particular, no difference in the Wechsler scores for reading or arithmetic (Table 2). The family backgrounds of 6 of the 14 children who were not fully assessed as initially hoped had been very unstable, reconfirming our earlier finding that the children in families who are easily contacted often differ significantly from those who are not, but this unstable family background was a feature in as many control families as index families. To avoid attrition bias, the study team received permission from the families from the outset and maintained regular contacts with them, and also obtained permission to receive relevant information about these children from the Office of National Statistics.

The authors of the initial report from Cambridge concluded that frequent low blood glucose levels in the period shortly after birth might be linked to later motor delay (and/or cerebral palsy) and cognitive delay, but the subsequent brief report said nothing about sensorimotor disability. Overt documented structural damage to the brain of a type common after preterm birth seems to provide an adequate explanation as to why at least 4 of the 6 index children in the current study and all 4 of the control children developed severe cerebral palsy. The only reason the same cannot be said for the other 2 index children is simply because no late cerebral ultrasound scan was ever done.

There was an eightfold variation in the incidence of recurrent “hypoglycemia” in the 5 centers that contributed to the Cambridge study, and the authors thought that this finding was probably due to the fact that staff held differing views as to the significance of the levels found. A fivefold difference was also found in the present 13-center study; however, in this study, attitudes toward low values did not differ so widely, and staff often got to know about the existence of a low value only after 6 to 8 hours, by which time the blood glucose level had often risen again already. There is good evidence to suggest that most of the observed intercenter difference can be explained by differences in early fluid management. It is a finding that also points to a strategy that could easily and safely (by increasing the early intake of dextrose and milk) reduce the number of infants with low blood glucose levels in the first few days of life.

One reason the article from Cambridge made such an impact was because it was followed within months by the publication of an article reporting that auditory and somatosensory-evoked brainstem potentials in 5 infants were delayed or blocked when the blood glucose level fell below the very same “threshold” value (≤2.5 mmol/L). Most clinicians have not noticed that subsequent studies using the same approach failed to find evidence for any such specific threshold. Despite this, it was not long before clinicians were extrapolating from this single observational study on preterm infants and assuming that the healthy term infant could be equally at risk from similar blood glucose levels even when the child seemed normal on clinical examination, which soon had an adverse impact on the care being given to the mothers of healthy infants trying to initiate lactation. We agree with the late Marvin Cornblath, who believed that the “adaptive fluctuations occurring in the first days after birth... should not be designated as ‘hypoglycemia,’ with its connotation of disease,” and we have not used this word to describe the low levels seen in this study.

It would be unwise to assume that low blood glucose levels cannot be damaging in the preterm infant even in the absence of overt recognizable signs, simply because this study has failed to replicate the earlier study from Cambridge. All that the current study can do is show that the danger threshold must be lower than many had come to think it was. Nevertheless, future studies will need to be large because detectable damage was not seen in the present region-wide study in which most infants were getting at least 6 mL/kg of intravenous 10% dextrose per hour by the time they were 4 days old, and only 2% had a documented level of <2 mmol/L on at least 3 different days in the first 10 days of life. The long-term outcome of the 389 infants in the recent European NIRTURE trial designed to investigate whether an early fixed-dose insulin infusion combined with variable glucose support to maintain normoglycemia would reduce mortality will go some way to show just how large such a study would need to
be, because this trial used continuous subcutaneous glucose monitoring and highlighted a serious underestimate of occurrence of blood glucose level of $\leq 2.5 \text{ mmol/L}$ by current routine monitoring practices, compared with continuous monitoring (5% vs 23%) in infants with birth weights $< 1500 \text{ g}$ during the first week of life.

**CONCLUSIONS**

Lucas et al wrote in their original article that “the association between modest hypoglycaemia and poor neurodevelopment reported here might not be causal and might reflect our failure to adjust adequately for confounding factors.”

They also stressed in a later letter “the difficulty of proving causation when an observational approach is used,” saying that “when such observations generate hypotheses or legitimate clinical concerns, this should stimulate future studies.”

We have now performed such a study and found no evidence to support that recurrent low blood glucose levels of $\leq 2.5 \text{ mmol/L}$ (45 mg/dL) pose a hazard to preterm infants.

**ACKNOWLEDGMENTS**

It was the neonatal nurses in every maternity unit in the north of England who, with the support of their medical colleagues, made the launch of this prospective, region-wide project possible. We are equally grateful for the encouragement and support of all of our pediatric colleagues for the past 20 years. All authors share responsibility for the reported research and for this report. The psychometric assessment of the 15-year-olds was organized by Dr. Kelly and undertaken by Ms. Brunskill. Dr. Tin is the guarantor. The authors also wish to acknowledge the huge debt they owe to the late Dr. Edmund Hey, who made the financing of the follow-up study possible and also helped with the initial drafting of this article.

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/20/7/e6
Neonatal Hypoglycemia
Jane E. McGowan, MD*

OBJECTIVES
After completing this article, readers should be able to:
1. Describe the most common cause of prolonged neonatal hypoglycemia.
2. List the signs of hypoglycemia.
3. Describe the condition that has been implicated as a mechanism of hypoglycemic brain injury.

Case Study
A term male infant was born after an uneventful pregnancy to a 28-year-old gravida I woman who had no evidence of hyperglycemia and no chronic diseases. The infant had Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. His growth parameters were in the normal range, with weight at the 60th percentile, head circumference at the 50th percentile, and length at the 50th percentile. The baby was taken to the well baby nursery, examined and bathed, and then taken to the mother for nursing at about 2 hours of age. He appeared slightly jittery at that time and was not very interested in nursing or very aware.

A blood glucose concentration of 1.39 mmol/L (25 mg/dL) was obtained using a One Touch® instrument. The baby was fed 25 mL of 5% dextrose in water. The blood glucose concentration obtained 1 hour later was 2.22 mmol/L (40 mg/dL), and the baby nursed for about 5 minutes at each breast with apparent satisfaction. Jitteriness and “lack of interest” were improved.

Normal nursery routine was followed, with no comment in the chart by the nursing staff about the infant’s feeding or behavior until the second day of life when he again appeared jittery and fussy. Glucose concentration at that time was 1.11 mmol/L (20 mg/dL). The infant was fed by breast or bottle (routine 20 kcal/oz house formula) alternating every 2 hours, and clinical signs improved. One Touch® glucose concentrations obtained over the next 24 hours were variable, but overall the concentration increased, with a predischARGE, preprandial value of 2.78 mmol/L (50 mg/dL).

The family failed to return to the hospital clinic the next day, but did see their primary care physician on the fifth day of life at which time the infant acted hungry, was noted to be “very active,” and weighed 11.3 g more than birthweight. At 2 weeks of life, the parents noted the infant to be very fussy and jittery and to experience staring spells. At a local emergency department, he was noted to have lost weight, appeared somnolent but fussy when aroused, and started having tonic-clonic jerking movements of all extremities. A “glucose concentration” was less than 0.55 mmol/L (10 mg/dL). The infant was treated with intravenous glucose, and the apparent seizure resolved. Over the next several weeks, the infant returned to the emergency department several times with similar episodes.

When finally examined by the primary care physician, the infant had gained 283.5 g and appeared “puffy.” An “office glucose concentration” was 1.94 mmol/L (35 mg/dL). The infant was referred to a pediatric endocrinologist, who noted that the infant’s weight was approaching the 90th percentile, there was definite hepatomegaly, and the infant appeared “apathetic.” In the hospital, several serum glucose concentrations were measured at less than 2.22 mmol/L (40 mg/dL), with plasma insulin concentrations all greater than 144 pmol/L (20 mcU/mL).

The infant was treated with diazoxide with only limited success over the next 3 months. Development continued but was “slow.” He was treated in the local emergency department three times for tonic-clonic seizures, all requiring intravenous glucose to correct severe hypoglycemia. At 5 months of age, the infant underwent a subtotal pancreatectomy. While recovering, he had a severe, prolonged seizure and was noted to be in shock, requiring two rounds of resuscitation. Escherichia coli meningitis was diagnosed and treated successfully.

At 1 year of age, the infant showed little developmental gain from 6 months of age. At 5 years of age, he exhibited extremely poor growth, had diabetes mellitus that necessitated insulin treatment, and required pancreatic enzyme replacement with feedings to treat malabsorptive diarrhea. He was almost completely deaf and had marked developmental delay. His parents sought legal counsel, claiming that the treating physicians in the birth hospital failed to diagnose a “hyperinsulinism” condition that then led to delayed diagnosis and treatment, followed by severe neurologic damage.

Questions to consider (feel free to send in your answers to these questions and any questions of your own for the “experts” to consider and discuss about this case):
1. What is the likely diagnosis for this infant’s hypoglycemia?
2. What diagnostic tests could have been done in the birth hospital to determine whether the infant had

ABBREVIATIONS
AGA: appropriate for gestational age
ATP: adenosine 5’-triphosphate
IDM: infant of a diabetic mother
IGUR: intrauterine growth retardation
LGA: large for gestational age
NMDA: N-methyl-D-aspartate
SGA: small for gestational age

*Associate Professor of Pediatrics, MCP Hahnemann University and St. Christopher’s Hospital for Children, Philadelphia, PA.
transient or persistent hypoglycemia?

3. What could have been done prior to discharge from the birth hospital to provide evidence of the infant’s ability to maintain a normal blood glucose concentration with a normal feeding schedule?

4. What did the pancreatic pathology examination likely show at the time of subtotal pancreatectomy?

5. How would you assess the clinical outcome in relation to the primary diagnosis and its complications versus the E coli meningitis and shock?

William W. Hay, Jr, MD
Coeditor

Introduction

Glucose is the major source of energy for organ function. Although all organs can use glucose, the human brain uses it almost exclusively as a substrate for energy metabolism. Because cerebral glycogen stores are limited, maintenance of adequate glucose delivery to the brain is an essential physiologic function. The high brain-to-bodyweight ratio in the newborn results in a proportionately higher demand for glucose compared with the capacity for glucose production than that encountered in the adult, with cerebral glucose use accounting for as much as 90% of total glucose consumption. Although alternate fuels, such as lactate and ketone bodies, can be used as a substrate for energy production, the newborn’s immature counterregulatory response limits the availability of these molecules. Thus, newborns are extremely susceptible to any condition that impairs the establishment of normal glucose homeostasis during the transition from intrauterine to independent extraterine life.

Glucose Homeostasis in Utero

Glucose is one of the major substrates for fetal metabolism. Under normal conditions (ie, normal maternal glucose levels), virtually all of the glucose used by the fetus is supplied from the maternal circulation via facilitated diffusion across the placenta. This results in a fetal blood glucose concentration of approximately 70% of the maternal value. Although the enzymes necessary for both gluconeogenesis and glycogenolysis are present in the human fetus by the end of the first trimester, several studies have demonstrated that there is no significant glucose production in the fetus unless there is a sustained decrease in umbilical glucose uptake. Glucose utilization rates in the fetus have been estimated at 4 to 6 mg/kg per minute. Approximately 60% to 70% of fetal glucose utilization is accounted for by oxidation of glucose carbon to CO₂, with the remainder available for synthesis of glycogen and other macromolecules. In the human fetus, oxidation of glucose accounts for approximately 80% of fetal oxygen consumption, demonstrating that glucose is the major substrate for fetal oxidative metabolism.

The rate at which the fetus uses glucose is primarily a function of glucose concentration, although changes in insulin concentration may have a modest influence as well. Studies have demonstrated that levels of fetal pancreatic insulin secretion correlate with changes in fetal glucose concentration, but the pancreatic response is blunted compared with the newborn or adult. Insulin secretion in response to fetal hyperglycemia increases glucose utilization and oxidation rates, but it has little effect on fetal metabolic rate or the rate of oxygen consumption, suggesting that oxidation of other substrates is reduced under these conditions. Decreased oxidation of substrates such as amino acids and lactate results in increased availability of those substrates for tissue accretion and may account in part for the increased somatic growth associated with fetal hyperinsulinemia.

In animal models, administration of glucagon does not appear to have a direct effect on fetal glucose metabolism. However, the ratio of insulin to glucagon in the fetal circulation plays a critical role in regulating the balance between glucose consumption and energy storage. The high insulin:glucagon ratio in the fetal circulation results in activation of glycogen synthesis and suppression of glycogenolysis by regulating the activity of the hepatic enzymes used for these processes. Predominance of insulin maintains glycogen synthase in its active form and glycogen phosphorylase in its inactive form via cAMP-dependent effects on specific protein kinases and phosphorylases, thus enhancing glycogen synthesis and minimizing glycogenolysis. In most species, including humans, hepatic glycogen stores accumulate slowly during early and midgestation, with a rapid increase in hepatic glycogen content occurring during the last 30% of fetal life. The marked increase in glycogen synthesis during this period is associated with an increase in circulating concentrations of both insulin and cortisol. Because the increase in cortisol seems to be necessary for maximal activation of glycogen synthase, fetal adrenal dysfunction may limit hepatic glycogen accumulation late in gestation. Under conditions associated with decreased fetal glucose concentrations and increased glucagon secretion, such as chronic hypoglycemia or hypoxemia, glycogen phosphorylase is activated, and synthase is converted to its inactive form, thereby suppressing glycogen synthesis and stimulating glycogenolysis with subsequent depletion of fetal glycogen stores. The high insulin:glucagon ratio also suppresses lipolysis, which allows for additional energy to be stored in the form of subcutaneous fat. Thus, the fetal hormonal and metabolic milieu establishes a ready substrate supply that can be used during the metabolic transition from fetus to newborn.

Glucose Homeostasis in the Newborn

The relative dependence of the fetus on a constant supply of maternal glucose necessitates significant changes in regulation of glucose metabolism at birth following the abrupt interruption of umbilical glucose delivery. Although the exact trigger is unknown, a number of physiologic changes equip the newborn for maintenance of glucose homeostasis. Increased catechol-
amine concentrations immediately following delivery stimulate glucose secretion, with a subsequent decrease in the insulin:glucagon ratio. Glycogen synthase is inactivated and glycogen phosphorylase is activated, leading to stimulation of glycogenolysis and inhibition of glycogen synthesis. Release of glucose from glycogen provides a rapidly available source of glucose for the newborn in the first few hours postpartum. However, it has been estimated that term infants have only enough hepatic glycogen to maintain the glucose supply for about 10 hours. Therefore, other mechanisms are required to maintain glucose homeostasis. The high glucagon:insulin ratio postpartum also induces synthesis of the enzymes required for gluconeogenesis. With the combination of the release of fatty acids stimulated by the high catecholamine concentrations that leads to a marked increase in glycerol availability and the availability of free amino acids in the circulation, the infant becomes capable of significant gluconeogenesis by 4 to 6 hours of life. However, enzyme activities do not reach adult levels until 1 to 2 weeks of age. Basal glucose utilization rates in the newborn infant are 4 to 6 mg/kg per minute, almost twice the weight-specific rates in adults. During the first few hours of life, blood glucose concentrations fall from the fetal value, which reflects the mother’s blood glucose concentration, to as low as 1.7 mM/L (30 mg/dL) before the infant attains the metabolic transition to independent glucose production and establishes postnatal glucose homeostasis. Until an exogenous supply of substrate is provided, either by enteral feedings or administration of intravenous fluids, hepatic glucose output serves as the most significant source of glucose to meet metabolic demands. To maintain normal levels of hepatic glucose production, the infant must have adequate stores of glycogen and gluconeogenic precursors (eg, fatty acids, glycerol, amino acids, and lactate), appropriate concentrations of the hepatic enzymes required for gluconeogenesis and glycogenolysis, and a normally functioning endocrine system. Absence of any of these requirements leads to disruption of glucose homeostasis, most commonly resulting in neonatal hypoglycemia.

**Incidence, Diagnosis, and Clinical Presentation**

**INCIENCE**

Estimates of the incidence of hypoglycemia in the newborn depend both on the definition of the condition and the methods by which blood glucose concentrations are measured. The overall incidence has been estimated at 1 to 5 per 1,000 live births, but it is higher in at-risk populations. For example, 8% of large-for-gestational-age infants (primarily infants of diabetic mothers [IDMs]) and 15% of preterm infants and infants who have intrauterine growth retardation (IUGR) have been reported as having hypoglycemia; the incidence in the entire population of “high-risk” infants may be as high as 30%.

**LABORATORY DIAGNOSIS**

The concentration of blood glucose at which the diagnosis of neonatal hypoglycemia should be made has been highly controversial. Hypoglycemia in term infants has been defined as a blood glucose value of less than 2.0 mM/L (<35 mg/dL) or as a plasma glucose value of less than 2.2 mM/L (<40 mg/dL). However, a recent survey of pediatricians in the United Kingdom demonstrated no consensus as to the level of blood glucose that they considered “hypoglycemia”. They cited concentrations ranging from 1 mM/L (20 mg/dL) to 4 mM/L (70 mg/dL) as the lower limit of normal. Further, definitions of hypoglycemia are based primarily on population studies of blood or plasma glucose concentrations during the first 48 to 72 hours of life, with hypoglycemia being defined as a blood glucose level more than 2 standard deviations below the population mean. Such definitions have only limited physiologic significance. Physiologically, hypoglycemia is present when glucose delivery is inadequate to meet glucose demand and can occur over a range of glucose concentrations, depending on the status of the infant. For example, a 2-hour-old healthy infant who has a blood glucose of 1.7 mM/L (30 mg/dL) might not demonstrate impaired organ function, but a stressed infant might demonstrate physiologic hypoglycemia at a blood glucose concentration of 2.8 mM/L (50 mg/dL) if the rate of glucose delivery to specific organs (eg, the brain) is less than the rate of glucose utilization. No studies to date have established an absolute blood glucose concentration at which short- or long-term organ dysfunction invariably occurs, although animal studies suggest that concentrations less than 1 mM/L (<20 mg/dL), if sustained over a number of hours, may be associated with inevitable brain injury. Without specific evidence to support an absolute threshold value, no single blood glucose value can be used to define physiologic hypoglycemia.

The definition of “normal” blood glucose concentrations for a given population of newborns also depends on the feeding practices in that population. For example, the mean value for normal blood glucose concentrations in term infants determined from studies 30 years ago was significantly lower than values determined in the past 10 years. This is not because of a change in neonatal physiology, but because pediatricians no longer follow the practice of withholding feedings from healthy newborns for a prolonged period after delivery. Rather than reflecting “normal” neonatal glucose homeostasis, these early values demonstrated the effects of the interference of medical practitioners in the normal transition to postnatal metabolism. Similarly, early data that demonstrated lower blood glucose values in populations of preterm infants compared with term infants was interpreted erroneously to mean that low-birthweight infants tolerated hypoglycemia better than normal-weight neonates. In fact, these data reflected failure of hepatic glucose production in preterm infants in response to an inadequate supply of exogenous substrate. At that time, standard feeding practices had not been established for
this population, and reliable intravenous (IV) nutrition was not available. Finally, the time at which the blood glucose concentration is measured affects the value considered “normal”; blood glucose concentrations increase over the first 24 to 48 hours of life in healthy term infants, probably as a result of both the increasing volume of enteral feeding and initiation of gluconeogenesis. Thus, a value that would be considered “low normal” at 3 hours of life might be termed “hypoglycemic” at 18 hours.

Making a firm diagnosis of hypoglycemia is complicated further by the limitations of methods used to measure blood glucose concentrations rapidly. Although the “gold standard” remains the hexokinase method used by many diagnostic laboratories, this approach is impractical as a screening tool because of the time required to process the sample and to perform the assay. Furthermore, if the sample is not transported rapidly to the laboratory and processed quickly, the glucose will be metabolized by red blood cells, thereby falsely decreasing the glucose concentration. Placing the specimen in a tube that contains a glycolytic inhibitor such as sodium fluoride can prevent this problem, but such tubes are either not readily available or simply not used.

Most nurseries use glucose oxidase/peroxidase chromogen test strips to screen high-risk newborns for low blood glucose concentrations. A drop of blood placed on the reagent-impregnated paper strip for the specified time will induce a color change that correlates with blood glucose concentration. The actual blood glucose concentration can be estimated by comparison with a standard chart or determined more precisely by “reading” the color of the strip with a reflectance colorimeter that has been calibrated using a standard solution. Although use of a reflectance colorimeter to read the test strips improves precision, multiple studies comparing various methods have found that the correlation between “real” blood glucose values and values obtained using test strips remains highly variable. This is especially true at low blood glucose concentrations.

Reagent strip results also are susceptible to variations in the technique used to obtain the sample (eg, variability in the amount of blood applied to the strip or contamination of the sample by residual isopropyl alcohol on the skin). It has been estimated that screening with reagent strips will detect approximately 85% of cases of hypoglycemia, although the false-positive rate may be as high as 25%. Thus, to ensure accurate detection of low blood glucose concentrations, a confirmatory sample should be sent to a central laboratory if a test strip value is consistent with hypoglycemia or if the test strip result is in the normal range but clinical findings raise the suspicion of hypoglycemia.

**CLINICAL PRESENTATION**

Although hypoglycemia often is classified as “symptomatic” or “asymptomatic”, these terms actually reflect the presence or absence of physical signs that accompany a low blood glucose concentration. A variety of signs may be seen in cases of severe or prolonged hypoglycemia and in infants who have mild-to-moderate hypoglycemia and are otherwise physiologically stressed. Most findings are nonspecific and result from disturbances in one or more aspects of central nervous system function. These include abnormal respiratory patterns, such as tachypnea, apnea, or respiratory distress; cardiovascular signs, such as tachycardia or bradycardia; and neurologic findings, including jitteriness, lethargy, weak suck, temperature instability, and seizures. Many of these signs can result from other common neonatal disorders, including sepsis, hypocalcemia, and intracranial hemorrhage. Hypoglycemia always must be considered in an infant who exhibits one or more of these signs because untreated hypoglycemia can have serious consequences, and the treatment is fast, relatively easy, and has limited side effects. However, given current standards for newborn care, most cases of hypoglycemia in the neonate are diagnosed during routine screening of infants considered to be at risk but who appear physiologically normal at the time of evaluation.

**Etiology**

**PREMATURITY AND IUGR**

The causes of neonatal hypoglycemia can be categorized according to associated disturbances in one or more of the processes required for normal hepatic glucose production that may lead to transient or prolonged episodes of hypoglycemia (Table 1). Hepatic glycogen stores are limited in both preterm infants, who have not experienced the period of rapid glycogen accumulation during late gestation, and small-for-gestational age (SGA) infants, who have not had adequate substrate supply available for glycogen synthesis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Duration of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity, intrauterine growth retardation</td>
<td>Transient*</td>
</tr>
<tr>
<td>Asphyxia, hypothermia</td>
<td>Transient</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Transient</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>Transient</td>
</tr>
<tr>
<td>Erythroblastosis fetalis</td>
<td>Transient</td>
</tr>
<tr>
<td>Exposure to beta-agonist tocolytics</td>
<td>Transient</td>
</tr>
<tr>
<td>Familial hyperinsulinism</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Prolonged</td>
</tr>
</tbody>
</table>

*Generally <7 d duration.
which puts these newborns at risk for hypoglycemia. IUGR due to placental insufficiency with preservation of normal head size puts an added demand on the infant’s already low glycogen stores because of the increased brain-to-bodyweight ratio. Postterm infants and infants of multiple gestations also may be at risk because of the presence of relative placental insufficiency. In addition to decreased glycogen availability, studies in preterm and IUGR infants have found altered patterns of insulin secretion, substrate metabolism, and hormonal responses to changes in blood glucose concentration compared with appropriate-for-gestational age (AGA) term infants.

Infants who have experienced perinatal stress due to asphyxia or hypothermia or who have increased work of breathing due to respiratory distress may have “normal” glycogen stores, but the amount of glycogen available may be inadequate to meet their increased requirement due to higher-than-normal levels of glucose utilization. Hypoglycemia may occur in these infants once available glycogen has been used to meet the initial postnatal metabolic demands, particularly if there has been a period of hypoxemia with associated rapid consumption of glucose via anaerobic metabolism.

It is uncommon for inadequate levels of gluconeogenic precursors to be a limiting factor in hepatic glucose production in the newborn because even preterm infants appear to have sufficient fatty acids, glycerol, amino acids, lactate, and pyruvate available. However, gluconeogenic enzymes are induced more slowly in preterm infants. Further, production of ketone bodies is relatively diminished in response to hypoglycemia. Term infants may have augmented release of ketone bodies when blood glucose decreases, but the concentrations of ketones correlate poorly with the degree of hypoglycemia. As a result, the contribution of gluconeogenesis to hepatic glucose production may be limited in some newborns.

**IDMS**

Several groups of infants are at increased risk for hypoglycemia due to alterations in hepatic enzyme functions that impair glycolysis, gluconeogenesis, or both. Hepatic function can be affected by a number of endocrine and metabolic disturbances, the most common being hyperinsulinism. IDMs may have increased secretion of pancreatic insulin because of exposure to increased maternal glucose concentrations in utero. Placental glucose transport is increased, leading to fetal hyperglycemia, which in turn stimulates secretion of insulin by the fetal pancreas. IDMs also have exaggerated pancreatic insulin secretion in response to a given glucose load compared with nonIDMs. Other diabetes-induced alterations in maternal metabolism, such as changes in serum amino acids, may play a role in the metabolic alterations found in IDMs.

After delivery, increased blood glucose concentrations no longer are present, but the hyperinsulinemia persists, thus maintaining a high insulin:glucagon ratio postnatally. As a result, glycogenolysis and lipolysis are inhibited, gluconeogenic enzymes are not induced, and hepatic glucose production remains at low levels in the face of decreasing blood glucose concentrations. Insulin also increases peripheral glucose utilization in insulin-sensitive tissues such as skeletal muscle, contributing to rapid depletion of available glucose. The combined effects of increased glucose utilization and inhibited hepatic glucose production result in hypoglycemia, which may persist for 24 to 72 hours before insulin secretion patterns normalize.

**ERYTHROBLASTOSIS FETALIS AND BETA-AGONIST TOCOLYTIC AGENTS**

Although maternal diabetes is the most common cause of hyperinsulinism in the newborn, postnatal insulin secretion may be abnormal due to several other disorders. Infants who have erythroblastosis fetalis have increased levels of insulin and an increase in the number of pancreatic beta cells. The mechanism for this development is unclear, but one possibility is that glutathione released from hemolyzed red cells inactivates insulin in the circulation, which triggers more insulin secretion and upregulates the beta cells. Exchange transfusions may exacerbate the problem because transfused blood usually is preserved with a combination of dextrose and other agents. During the exchange, the infant receives a significant glucose load, with subsequent exaggerated insulin response from the hyperplastic pancreas. At the end of the exchange, the rate of dextrose administration returns to baseline, but insulin levels remain elevated, leading to further hypoglycemia.

Use of beta-agonist tocolytic agents such as terbutaline also is associated with hyperinsulinemia in the newborn, especially if the agent was used for more than 2 weeks and was discontinued less than 1 week prior to delivery. Affected infants also appear to have reduced glycogen stores, which further aggravates the hyperinsulinemia and its effects on decreasing glucose concentrations.

**HYPERINSULINISM**

Hypoglycemia that persists for more than 5 to 7 days is uncommon and most often is due to hyperinsulinism. Some infants who have IUGR or perinatal asphyxia demonstrate hyperinsulinemia that may persist for as long as 4 weeks, but such cases are relatively rare, and the underlying mechanism is unclear. Several types of congenital hyperinsulinism have been described and are said to be the most common cause of hypoglycemia persisting beyond the first week of life.

The autosomal recessive form of congenital hyperinsulinism has been linked to a defect in the sulfonylurea receptor or K⁺-ATP channel. A single mutation on the short arm of chromosome 11 has been described in the Ashkenazi Jewish population, but cases in other ethnic groups have been associated with a number of other mutations in the same region. An autosomal dominant form of hyperinsulinemia also has been described. The mutation(s) responsible for the autosomal dominant form of hyperinsulinism has not yet been identified, but the disorder differs from the autosomal recessive form in that it does not appear to result
from abnormal sulfonylurea receptor function. A syndrome of congenital hyperinsulinemia and asymptomatic hyperammonemia associated with mutations in the glutamate dehydrogenase gene also has been described. Beckwith-Weidemann syndrome is associated with hyperplasia of multiple organs, including the pancreas, with consequent increased insulin secretion. Rarely, hyperinsulinemia may result from localized islet cell adenomas within an otherwise normal pancreas.

**INBORN ERRORS OF METABOLISM**

Inborn errors of metabolism may affect either the availability of gluconeogenic precursors or the function of the enzymes required for production of hepatic glucose. Metabolic defects that may present with hypoglycemia include some forms of glycogen storage disease, galactosemia, fatty acid oxidation defects, carnitine deficiency, several of the amino acidopathies, hereditary fructose intolerance (fructose-1,6-diphosphatase deficiency), and defects of other gluconeogenic enzymes. Finally, endocrine disorders such as hypopituitarism and adrenal failure also can result in hypoglycemia because of the absence of the appropriate hormonal response to hypoglycemia and subsequent failure to activate hepatic glucose production. However, these conditions are very rare and should be considered after ruling out more common etiologies.

**DETERMINING ETIOLOGY**

Obtaining a careful perinatal history is the first step in determining the etiology of hypoglycemia in the newborn. The presence of risk factors, such as abnormal results on a maternal glucose tolerance test, maternal administration of drugs associated with neonatal hypoglycemia, or prematurity, makes the diagnosis relatively simple. Growth parameters should be plotted to establish if the infant is SGA, AGA, or LGA. Sepsis should be suspected strongly in the term infant who has hypoglycemia but no other apparent risk factors. If hypoglycemia persists for more than 1 week, the possibilities of hyperinsulinemia, other endocrine disorders, and inborn errors of metabolism should be investigated, especially if the hypoglycemia is refractory to standard treatment.

Unfortunately, it often is difficult to document hyperinsulinemia because insulin levels must be drawn during episodes of hypoglycemia to demonstrate the presence of inappropriate insulin secretion. Levels of the binding protein for insulin-like growth factor 1 (IGFBP-1) are decreased in the presence of hyperinsulinemia, making measurement of serum levels of IGFBP-1 useful in confirming the diagnosis of hyperinsulinemia. Serum and urine tests for specific metabolic and endocrine disorders, such as serum amino acid profiles and measurement of cortisol and growth hormone levels, also may be necessary to elucidate the etiology of neonatal hypoglycemia.

**Management**

The goals in treating the infant who has hypoglycemia are to normalize blood glucose concentrations as quickly as possible and to avoid further episodes of hypoglycemia by providing adequate substrate until normal glucose homeostasis can be established. The method chosen to achieve this goal is a function of both the clinical status of the infant and the suspected etiology of the hypoglycemia.

**ENTERAL FEEDING**

In term infants who have asymptomatic mild hypoglycemia, an initial attempt at enteral feeding may be successful in reaching target blood glucose values. Although a prompt increase in blood glucose concentrations can be achieved following a feeding with a 5% dextrose and water solution, the dextrose is metabolized rapidly, and hypoglycemia may recur before normal feedings can be established. Use of a standard infant formula will provide not only carbohydrate in the form of lactose but also protein and fat, which are metabolized more slowly and, therefore, will provide a sustained supply of substrate. Fat intake also decreases cellular glucose uptake and stimulates gluconeogenesis, further contributing to a restoration of normal glucose homeostasis. It is estimated that blood glucose concentrations should increase by approximately 1.67 mmol/L (30 mg/dL) within the first hour after a feeding of 30 to 60 mL of standard infant formula.

**IV THERAPY**

Infants whose blood glucose concentrations normalize following an enteral feeding should continue to have blood glucose concentrations checked before each feeding for 12 to 24 hours. If the postprandial concentration is normal, but the value before the next feeding is again in the hypoglycemic range, enteral feeding should be considered a failure, and the infant is a candidate for IV therapy. Prompt provision of IV glucose in these circumstances will avoid repeated episodes of preprandial hypoglycemia. This may be important because follow-up studies of infants who have recurrent hypoglycemia indicate that multiple episodes of low blood glucose concentrations are more likely to be associated with adverse neurodevelopmental outcomes than a single episode.

IV therapy should be the first treatment modality used in symptomatic infants, infants unable to tolerate enteral feedings, and those in whom the disturbance in glucose homeostasis is severe or is expected to last more than a few hours. The latter category includes preterm infants, infants who have IUGR, infants of women who have poorly controlled diabetes, and infants who have underlying etiologies for hypoglycemia, such as sepsis, known or suspected inborn errors of metabolism or endocrine defects, or erythroblastosis.

Administration of an initial bolus of 200 mg/kg of 10% dextrose and water (2 mL/kg of D10W) should be followed by continuous infusion of dextrose calculated to deliver 5 to 8 mg/kg per minute of glucose (ie, a rate equivalent to the glucose utilization rate of a healthy infant). The “mini-bolus” approach has been shown to return blood glucose concentration to normal more rapidly than a constant infusion alone. The
“mini-bolus” dose also is designed to avoid overshooting the desired glucose concentration. By limiting the amount of glucose given as a bolus, it is possible to avoid inducing iatrogenic hyperglycemia, which might stimulate excess insulin secretion and induce rebound hypoglycemia. The blood glucose concentration should be checked approximately 30 minutes after the bolus, then every 1 to 2 hours until stable and in the normal range. If a subsequent value falls in the hypoglycemic range, the bolus should be repeated and the infusion rate increased by 10% to 15%. It is not uncommon for infants who have transient or sustained hyperinsulinemia to require as much as 12 to 15 mg/kg per minute of IV glucose to maintain normoglycemia. In such cases, it may be necessary to place an umbilical venous catheter or a peripheral central venous catheter (so-called PIC line) to allow administration of IV solutions with dextrose concentrations greater than 12.5%.

Unless there are concerns about fluid overload or the ability to tolerate enteral nutrition, infants requiring IV therapy for hypoglycemia should be permitted to continue feedings. There are several benefits to this practice. First, it will allow an easier transition from a parenteral to an enteral source of carbohydrate once blood glucose concentrations have stabilized. Second, providing some carbohydrate as galactose (one of the sugars that comprise lactose) may be useful in IDMs and other infants who have hyperinsulinemia; studies have shown that the pancreatic insulin response to galactose is less than the response to an equivalent amount of glucose. When a normal blood glucose concentration has been established and the requirement for IV glucose has been stable for 12 to 24 hours, the infant can be weaned from this therapy by measuring preprandial blood glucose concentrations and decreasing the infusion rate by 10% to 20% each time the blood glucose is greater than 2.8 to 3.4 mmol/L (>50 to 60 mg/dL). Failure to tolerate weaning from IV glucose indicates the presence of a pervasive disorder, such as a metabolic defect or idiopathic hyperinsulinemia, and should prompt further evaluation.

OTHER AGENTS
Several other agents have been used to treat refractory hypoglycemia, most often encountered in one of the hyperinsulinemic states (Table 2). Corticosteroids (hydrocortisone, 5 to 15 mg/kg per day in two to three divided doses, or prednisone, 2 mg/kg per day) are associated with decreased peripheral glucose utilization and increased blood glucose concentrations, but they have a variety of other metabolic effects that must be considered. Administration of corticosteroids as an adjunct to IV glucose may be useful when glucose requirements are greater than 15 mg/kg per minute.

Glucagon will produce a rapid rise in blood glucose in infants who have adequate glycogen stores, but this is only a transient effect, and caregivers must be prepared to manage hypoglycemia when it recurs. Preterm infants and infants who have IUGR have limited glycogen stores and are unlikely to experience an increase in blood glucose concentration following administration of glucagon. An initial dose of 30 mcg/kg may produce a response in some infants, but those who have hyperinsulinemia may require a 10-fold higher dose to overcome the effects of high circulating insulin levels and stimulate glycogenolysis. Administration of glucagon is most useful in those infants who have severe hypoglycemia as a temporizing measure until stable IV access can be obtained (eg, while awaiting the arrival of a transport team).

Several other agents may be valuable for management of infants in whom the diagnosis of hyperinsulinemia is confirmed and who remain persistently hypoglycemic in spite of administration of IV glucose at 15 to 20 mg/kg per minute. Diazoxide at a dose of 5 mg/kg every 8 hours will inhibit pancreatic insulin secretion. Somatostatin or its long-acting analogue octreotide also inhibits insulin release as well as growth hormone and glucagon secretion and is used most often preoperatively in infants requiring pancreatectomy for refractory hypoglycemia and hyperinsulinemia. Subtotal (95%) or near-complete pancreatectomy may be required to manage cases of hyperinsulinemia due to gene mutations or islet cell adenomas. However, hypoglycemia recurs in up to 33% of surgically treated patients, and 40% to 60% of infants who have hyperinsulinemia may require a 10-fold higher dose to overcome the effects of high circulating insulin levels and stimulate glycogenolysis.

THERAPY | EFFECT | DOSAGE
--- | --- | ---
Corticosteroids | Decrease peripheral glucose utilization | Hydrocortisone 5 to 15 mg/kg per day or Prednisone 2 mg/kg per day
Glucagon | Stimulates glycogenolysis | 30 mcg/kg if normal insulin, 300 mcg/kg if increased insulin
Diazoxide | Inhibits insulin secretion | 15 mg/kg per day
Somatostatin (long-acting: octreotide acetate) | Inhibits insulin and growth hormone release | 5 to 10 mcg/kg every 6 to 8 h
Pancreatectomy | Decreases insulin secretion | ---

ENDOCRINOLOGY
Hypoglycemia

TABLE 2. Adjunct Therapies for Hypoglycemia

Diazoxide Inhibits insulin secretion 15 mg/kg per day

Glucagon Stimulates glycogenolysis 30 mcg/kg if normal insulin

Corticosteroids Decrease peripheral glucose utilization

Pancreatectomy Decreases insulin secretion —

Hypoglycemia

THERAPY | EFFECT | DOSAGE
--- | --- | ---
Corticosteroids | Decrease peripheral glucose utilization | Hydrocortisone 5 to 15 mg/kg per day or Prednisone 2 mg/kg per day
Glucagon | Stimulates glycogenolysis | 30 mcg/kg if normal insulin, 300 mcg/kg if increased insulin
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Somatostatin (long-acting: octreotide acetate) | Inhibits insulin and growth hormone release | 5 to 10 mcg/kg every 6 to 8 h
Pancreatectomy | Decreases insulin secretion | ---

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Pancreatectomy Decreases insulin secretion —

Hypoglycemia

THERAPY | EFFECT | DOSAGE
--- | --- | ---
Corticosteroids | Decrease peripheral glucose utilization | Hydrocortisone 5 to 15 mg/kg per day or Prednisone 2 mg/kg per day
Glucagon | Stimulates glycogenolysis | 30 mcg/kg if normal insulin, 300 mcg/kg if increased insulin
Diazoxide | Inhibits insulin secretion | 15 mg/kg per day
Somatostatin (long-acting: octreotide acetate) | Inhibits insulin and growth hormone release | 5 to 10 mcg/kg every 6 to 8 h
Pancreatectomy | Decreases insulin secretion | ---
develop diabetes mellitus later in life.

Consequences of Hypoglycemia

HYPOGLYCEMIC BRAIN INJURY

Although hypoglycemia is associated with a number of physiologic changes, the most profound effects are seen in the brain, where glucose is the major substrate for energy metabolism and both local energy stores and the supply of alternate substrates are limited. Severe hypoglycemia in the newborn is associated with selective neuronal necrosis in multiple brain regions, including the superficial cortex, dentate gyrus, hippocampus, and caudate-putamen. The initiating events in hypoglycemic encephalopathy still are not understood completely, but brain injury appears to result from a number of processes that are initiated when blood glucose concentrations decrease (Figure). A moderate reduction in blood glucose concentration is associated with compensatory increases in cerebral blood flow that have been assumed to represent a means of maintaining delivery of cerebral glucose. In preterm newborns, such changes in cerebral blood flow may predispose to intraventricular hemorrhage and may have little effect on neuronal glucose supply because transfer of glucose across the blood-brain barrier depends on the activity of the glucose transporters on the vascular endothelium and cell membranes. Glucose transporter levels are decreased in the fetus and newborn compared with older infants and may be rate-limiting for cerebral glucose uptake.

If glucose supply to the brain is not maintained, there may be a decrease in cerebral electrical activity, membrane breakdown with release of free fatty acids, and altered amino acid metabolism, including increased production of glutamate. Glutamate, which is one of the excitatory amino acid neurotransmitters found only in the central nervous system, is believed to play a major role in the pathophysiology of hypoglycemic brain injury. Hypoglycemia is associated with increased glutamate concentrations in the synaptic cleft, most likely due to a combination of increased glutamate release from presynaptic neurons and decreased adenosine 5'-triphosphate (ATP)-dependent glutamate uptake by glial cells. Glutamate binds to postsynaptic receptors, triggering release of second messengers via the metabotropic glutamate receptors and changes in transmembrane ion fluxes via the ionotropic glutamate receptors. Although there are several types of ionotropic receptors, the N-methyl-D-aspartate (NMDA)-type glutamate receptor, which is associated with an ion channel that transports sodium and calcium into the cell and potassium out of the cell, predominates in immature brain. In all species studied, including humans, the number of functional NMDA receptors increases during brain development, subsequently decreasing to adult levels.

The increased number of NMDA receptors in the late fetal and early newborn periods most likely reflects the role of the receptor as one of the primary mediators of long-term potentiation, a process that is associated with synaptogenesis and memory formation. NMDA receptor activity also may be involved in regulating the process of apoptosis, or programmed cell death, via changes in cytoplasmic and nuclear calcium concentrations. In the human fetus, the third trimester of fetal development and early neonatal period are characterized by active formation and modification of synaptic connections and arborization of dendrites associated with increased NMDA receptors. Thus, normal levels of NMDA receptor activity are critical to the development of the immature brain. However, excess activation of NMDA receptors by glutamate increases cytoplasmic concentrations of...
Hypoglycemia also could exacerbate brain injury during periods of cerebral hypoxia in immature brain. As in hypoglycemia, cerebral hypoxia is associated with depletion of high-energy phosphates, increased extracellular glutamate concentrations, activation of ionotropic glutamate receptors, and increased intracellular sodium and calcium. In addition, anaerobic glycolysis during hypoxia accelerates depletion of glucose in the brain. Thus, the combination of hypoglycemia and hypoxia might be expected to act synergistically in producing neuronal injury. Although hypoglycemia appears to be neuroprotective during cerebral ischemia in adults, studies in immature animals have demonstrated that concurrent hypoglycemia exacerbates hypoxic-ischemic brain injury, possibly by accelerating depletion of high-energy phosphates. Hypoglycemia also abolishes hypoxic vasodilatation of cerebral blood vessels, thus impairing compensatory mechanisms that might otherwise improve oxygen delivery to the brain during periods of hypoxemia. Although further investigation is necessary, these results indicate that maintenance of normoglycemia is especially critical in infants at risk for episodes of hypoxemia, such as those who have significant respiratory distress.

**CLINICAL CONSEQUENCES**

The physiologic disturbances associated with acute hypoglycemia in the newborn result in a stress response, with release of catecholamines and glucagon and subsequent lipolysis and glycogenolysis in an attempt to increase substrate availability for normal metabolic processes. Thus, even in asymptomatic hypoglycemia, there are significant short-term effects on the infant that may result in depletion of endogenous substrate, leaving the infant unprepared to handle subsequent physiologic stress. In term infants, a brief period of increased sympathetic activity and altered hepatic metabolism usually is tolerated well. However, in the preterm or SGA infant, the added physiologic stress associated with a low blood glucose concentration may be sufficient to precipitate cardiorespiratory instability and complicate acute management significantly. Prompt, rapid normalization of low blood glucose concentrations is required to minimize the hormonal and metabolic derangements. If a normal blood glucose concentration can be achieved in a timely manner, the acute effects of a single episode of hypoglycemia can be minimized.

The long-term effects of neonatal hypoglycemia remain controversial. Repeated episodes of symptomatic hypoglycemia, as are seen in infants who have persistent hyperinsulinism, have been associated with selective neuronal necrosis and long-term impairment of cognitive and motor function. Early studies also reported poor neurodevelopmental outcomes in IDMs. However, more recent data suggest that hypoglycemia alone does not alter long-term outcome in IDMs; rather, adverse outcomes were related to the presence of congenital anomalies.

Very few data are available regarding the long-term outcome in the vast majority of hypoglycemic infants who have asymptomatic hypoglycemia that is detected on routine screening and is treated promptly. Studies in normal adults have shown that cognitive function is impaired during mild insulin-induced hypoglycemia (blood glucose values < 3.4 mmol/L [<60 mg/dL]). Adult diabetics who have a history of recurrent episodes of hypoglycemia have been found to have persistent cognitive deficits as well as mild cortical atrophy, findings that have not been observed in diabetics who have not experienced significant hypoglycemia.

Most studies in newborns, although unavoidably limited in scope, have failed to demonstrate any long-term sequelae in term infants who have experienced brief episodes of hypoglycemia. Changes in brainstem auditory evoked responses (BAERs) were reported in several infants (1 to 5 d old) during episodes of hypoglycemia of unspecified etiology. Abnormal BAERs were detected at blood glucose concentrations ranging from 0.7 to 2.5 mmol/L (12 to 45 mg/dL), and in two infants they remained abnormal for several hours after glucose had been administered. How-
ever, no long-term follow-up was reported on these infants. A second study, which analyzed factors affecting outcome at 18 months of age in a cohort of preterm infants, found that those who had at least one blood glucose value less than 2.6 mmol/L (46 mg/dL) on 5 or more days had significantly lower scores on standardized tests of mental and motor development and a threefold higher incidence of cerebral palsy than those who had fewer episodes of hypoglycemia or those who had experienced a single episode of more severe hypoglycemia. The differences remained significant when other risk factors such as birthweight and intraventricular hemorrhage were accounted for. Thus, there is evidence to suggest that mild-to-moderate hypoglycemia may affect outcome, at least in high-risk infants.

Conclusion
Disturbances of glucose homeostasis that result in hypoglycemia are common among newborns. Awareness of risk factors that predispose infants to hypoglycemia allows for screening of those at risk so that clinically undetectable hypoglycemia can be treated promptly, thereby preventing the development of severe or symptomatic hypoglycemia, which is associated with adverse outcomes. However, management of high-risk infants is complicated by the lack of a consensus on the blood glucose value that constitutes hypoglycemia as well as the inaccuracies in methods used to measure blood glucose values. A further unresolved issue is whether asymptomatic hypoglycemia is associated with permanent effects on brain function in the newborn. No conclusive studies demonstrate long-term effects of asymptomatic hypoglycemia in term infants, but it is likely that hypoglycemia contributes to abnormal neurodevelopmental outcome in infants who have other risk factors for brain injury, such as prematurity or hypoxic-ischemic brain injury. In these infants, maintaining blood glucose concentrations well above the threshold for hypoglycemia may improve neurologic outcome. Further studies are necessary to determine the consequences of hypoglycemia in term infants.

SUGGESTED READING
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Jane E. McGowan
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DOI: 10.1542/pir.20-7-e6

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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?

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 1
Levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review of randomized controlled trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized controlled trial (with narrow confidence interval)</td>
</tr>
<tr>
<td>1c</td>
<td>All cases affected before intervention, some or none affected after intervention</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review of cohort studies</td>
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<tr>
<td>2b</td>
<td>Individual cohort study (including low-quality randomized controlled trial)</td>
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<td>2c</td>
<td>‘Outcomes’ research</td>
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<tr>
<td>3a</td>
<td>Systematic review of case-control studies</td>
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<tr>
<td>3b</td>
<td>Individual case-control study</td>
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<tr>
<td>4</td>
<td>Case series (and poor-quality cohort and case-control studies)</td>
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<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’</td>
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Adapted with permission from reference 1

Table 2
Grades of recommendation

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<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies or extrapolations from level 2 or 3 studies</td>
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<tr>
<td>D</td>
<td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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Adapted with permission from reference 1

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

<table>
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<th>Birthweight (g)</th>
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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, limpingness 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-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 IDM s 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. Stenninger 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.
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 neurologic 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

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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 COUNSELED 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).

REFERENCES


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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.