

**REVIEW ARTICLE:****Management of Neonatal Hypoglycaemia****Dr. Abdelhadi Abdelgabbar Abdelhadi**

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**Summary**

Neonatal Hypoglycaemia is an important and common problem which is readily diagnosed and should be actively sought and treated. Symptomatic hypoglycaemia is associated with poor prognosis and adverse developmental outcome. A moderate degree of persistent asymptomatic hypoglycaemia is associated with impaired motor and cognitive development. Therefore every effort should be directed towards identification of babies with asymptomatic low blood glucose levels and their prompt treatment. Every hospital with maternity and or neonatal unit must have clear guidelines to facilitate the screening and management of neonatal hypoglycaemia. This paper outlines the strategies for the management of neonatal hypoglycaemia.

**Key Words:** neonatal, hypoglycaemia, hyperinsulinaemia.

**Background and Pathophysiology**

The major fuel for the foetus and the newborn is glucose. <sup>(1)</sup> Alternate fuels like ketones, free fatty acids and lactate assume an important role during starvation but are produced in inadequate quantities. Although breast-fed infants are likely to have higher levels of alternative fuels <sup>(2)</sup>, there is no evidence that asymptomatic hypoglycaemia in this cohort of babies is less damaging to the newborn than in formula fed babies and the

operational threshold should be the same for both groups of babies. Persistent low blood sugar levels are associated with impaired motor and cognitive development even in asymptomatic babies. <sup>(3, 4)</sup>

Neonatal brain metabolism accounts for 80-85 % of total glucose consumption. <sup>(4, 5)</sup> The rate of brain utilisation of glucose in the newborn is ~ 4 - 8 mg / kg/minute. (D10% 60-120 ml /kg/day). Although all the neonatal organs and tissues can use glucose, the brain uses it almost exclusively as a substrate for energy metabolism. The combination of limited cerebral glycogen stores and the high brain-to bodyweight ratio in the newborn results in a proportionately higher demand for glucose compared with the capacity for glucose production. The newborn's immature counter regulatory response limits the availability of alternate fuels like ketones bodies and lactate. <sup>(6)</sup> Thus, it is not surprising that newborns are extremely susceptible to hypoglycaemia as a result of any process that impairs the establishment of normal glucose homeostasis during the transition from intrauterine to independent extra uterine life.

### Definition

For decades Neonatologist did not agree a definition for neonatal hypoglycaemia. <sup>(6)</sup> It is widely agreed now that the defined level of low blood glucose should constitute a threshold point rather than a diagnostic entity. The majority of the neonatal units worldwide have adopted an operational threshold of < 2.6 mmol/l (< 46 mg/dl) as the practical definition of neonatal hypoglycaemia. This threshold is based on the pioneering study by Lucas et al <sup>(7)</sup> who showed in a detailed metacentre study of 661 preterm infants that moderate persistent hypoglycaemia (plasma glucose concentration less than 2.6 mmol/l, significantly reduced the mental and motor developmental scores at 18 months (corrected age) and increased the incidence of neurodevelopmental impairment (cerebral palsy or

developmental delay) by a factor of 3.5 (95% confidence interval 1.3 to 9.4).

A more recent study from the Nederland's by P.L.P Brand et al <sup>(8)</sup> has shown that transient mild hypoglycaemia in healthy, term LGA newborns does not appear to be harmful to the psychomotor development at the age of 4 years. This highlights the fact that prompt treatment of neonatal hypoglycaemia is likely to be rewarded.

### **Aetiology of Neonatal Hypoglycaemia**

Neonatal hypoglycaemia may be caused by a number of processes. These are shown in table I In many babies more than one process may be operating with a common final pathway leading to hypoglycaemia (9). Reduced foetal stores of glycogen, hyperinsulinaemia, and limited glucose supplies are the main categories leading to neonatal hypoglycaemia as summarised in table (1). Increased glucose utilisation is another factor which is prominent in polycythaemia, cold stress, perinatal asphyxia and sepsis. (9) Septicaemic babies and babies with hypothermia, polycythaemia, and those with endocrinopathies are likely to have mixed mechanisms (10). Infants of diabetic mothers (IDM) worth a special note as their hyperinsulinaemia state may last for few days. (11) Low blood sugars in this group of babies should prompt frequent monitoring of the baby and the blood sugar levels till they are consistently above the operational threshold.

### **Symptoms of Hypoglycaemia**

If the at risk neonatal population are properly targeted with timely screening, then the majority of babies will be asymptomatic. However symptoms are often non-specific and may start as early as the first hour of life. <sup>(2)</sup> Common forms of presentations include jitteriness, lethargy, hypotonia, feeding intolerance, apnoea and cyanosis. Fits and altered level of

consciousness indicate either severe or prolonged degree of hypoglycaemia. <sup>(12)</sup>

The length of the period during which an individual baby continues to be at risk of developing hypoglycaemia varies with various aetiologies. <sup>(13)</sup> Therefore, careful history and examination as well as investigations when appropriate should be carried out to ascertain the cause of hypoglycaemia. In the majority of babies an identifiable risk factor is apparent and specialised investigations are not necessary. As a general rule recurrence of hypoglycaemia is unlikely in babies who are able to maintain consistent euglycaemia on enteral feeding which is appropriately spaced. Babies who have a single episode of profound hypoglycaemia with blood glucose level  $< 1.1$  mmol/l ( $< 20$  mg/dl) as well as those with hypoglycaemia lasting more than one week require further assessment for evidence of hyperinsulinaemia. More robust criteria are described by Aynsley Green et al <sup>(14)</sup> as summarised in table (6). Other endocrine disorders must also be excluded in babies with persistent hypoglycaemia unless they are clearly septicaemic during this period. The hyperinsulinaemia of the infants born to diabetic mothers is transient and in most cases will resolve within few days. Babies with severe perinatal asphyxia may rarely have persistent hypoglycaemia lasting more than a week. The preterm babies could be considered out of the at risk period when they are able to maintain normal blood sugar levels on 3-4 hourly enteral non supplemented feeding

## **Management lines**

### **1.Prevention of asymptomatic hypoglycaemia by intervention strategies in the at risk group:**

This includes early feeding whenever possible and avoidance of delay in intravenous glucose administration when it is clear that an (at risk) baby is unable to feed enterally. Healthy looking

babies should be put to breast as soon as possible after delivery and certainly not later than 30-60 minutes after birth. Formula fed babies should be offered a suitable formula within 30 minutes of their birth. Intra-gastric tube is a suitable mean of delivering milk to those babies who can tolerate enteral feeding but are unable to suckle due to their prematurity or other reasons. Mildly tachypnoeic babies who are unable to feed may tolerate nasogastric tube feeding. When the mother of a susceptible baby is not able to nurse the baby soon after birth either formula milk or intravenous glucose should be started as soon as possible. The choice will depend on the circumstances and the mother preference.

Oral glucose 5% should be avoided if at all possible as hypoglycaemia may be made worse. Glucose is metabolised rapidly following absorption and although a prompt rise is to be expected in the blood sugar level, this is transient and may be followed by reactive hyperinsulinaemia in the susceptible babies. Carbohydrates, fats and proteins are provided in milk which should be the natural choice <sup>(15)</sup>. Volume for volume the milk provides at least triple the amount of energy provided by Dextrose and water 5% oral solutions. Thus while 50 ml of milk provides at least 33 kcal, an equivalent amount of dextrose 5% gives 10 kcal only. Furthermore, proteins and fats are metabolized more slowly and, therefore, will provide a sustained supply of substrate <sup>(16)</sup>. Normal glucose haemostasis is restored more efficiently by fat intake as it decreases cellular glucose uptake and stimulates gluconeogenesis. An increase in blood glucose concentration by 1-2 mmol/l ( 18-35 mg/dl) is to be expected within an hour following enteral feeding with 30- 60 ml of breast milk or standard infant formula.

## 2. Screening of the neonates who are at higher risk of developing hypoglycaemia

The screening should target various at risk groups as detailed in table (2). The timing of the first blood sugar estimation and the frequency of subsequent tests is decided by the aetiology of the hypoglycaemia as well as the response of the baby to the initiated interventions and the level of blood sugar during the monitoring period. Hypoglycaemia may recur during the at risk <sup>(18)</sup> period and estimation of blood sugar levels should continue throughout this period and till the baby is able to maintain normal blood sugar levels on 3-4 hourly non supplemented oral feeds. Table (3) enlists other at risk groups who should be targeted at the appropriate time.

## 3. Early management of Asymptomatic Hypoglycaemia

Asymptomatic Babies who are discovered during the screening to have low blood sugars should be offered an attempt of breast, bottle, or nasogastric feeding provided their blood sugar is not dangerously low. Many Neonatologists will allow well babies with blood sugar level  $> 1.5$  mmol/l ( $> 27$  mg/dl) a trial of enteral feeding. The blood sugar for this group should be rechecked one hour after the completion of the enteral feed and if it remains below 2.6 mmol/l but above 1.5 mmol/l a further feed is offered and blood sugar rechecked one hour later. If hypoglycaemia persists an intravenous glucose 10% should be sited. Breast or formula feeding can continue as extra in this group of babies. A pre-prandial further check is indicated in babies who are able to maintain normal post-prandial glucose level following an enteral feed. Failure to maintain a normal glucose level  $> 2.6$  mmol/l ( $> 46$  mg/dl) necessitates an intravenous glucose infusion

A different approach is required in asymptomatic babies with markedly low levels of glucose defined as levels  $< 1.5$  mmol/l ( $< 27$  mg/dl). Such babies should be managed as an emergency with intravenous bolus (3 ml/kg) of dextrose 10% followed by an

infusion of dextrose 10% at the appropriate rate. Breast and bottle feeding should be deferred for few hours till the course and effect of hypoglycaemia are monitored.

#### **Frequency of subsequent blood sugar estimation:**

If the blood glucose concentrations normalize following an enteral feed, subsequent checks should continue before each feeding for 12 to 24 hours. When 3 consecutive preprandial blood sugar levels are consistently well above 2.6 mmol/l (>46mg/dl) in babies fed 2-3 hourly, the frequency of blood sugar estimation should be decreased gradually or discontinued. The algorithm in figure (1) should be followed provided the baby remains asymptomatic throughout the screening period.

Babies who are asymptomatic but require intravenous glucose due to failure of enteral feeding to correct hypoglycaemia or due to initial very low glucose concentration defined as glucose concentration <1.5 mmol/l (< 26.4mg/dl) require more frequent blood sugar checks. The first check should be one hour after the dextrose infusion has been set followed by hourly checks till 3 consecutive readings are well above 2.6 mmol/l (>46mg/dl). Further checks could be 2-3 hourly if euglycaemia is maintained. Any hypoglycaemic baby on intravenous infusion should continue to have hourly check with the appropriate steps to either increase the volume infused or the concentration of the dextrose. Increment in infused dextrose should be by 2 mg/kg/min. This is achieved by increasing the D10% by 30 ml/kg/day. If fluid overload is anticipated, higher concentrations of glucose should be used starting with 12% dextrose and proceeding in stepwise fashion to 14%, 18% and 22%. It is mandatory to recheck the blood sugar after one hour of any increment to make sure the hypoglycaemia is controlled. The cycle of increasing the infused glucose amount and rechecking the blood sugar should continue till normal levels are obtained. Weaning should follow a similar gradual process to avoid recurrence of the hypoglycaemia. Table

(4) sets the guidance for the preparation of various higher strengths of Dextrose. The Flow Chart in Figure (1) outlines a stepwise approach in the management of neonatal hypoglycaemia.

#### **4. Prompt treatment of symptomatic babies**

It is of vital importance to avoid repeated episodes of preprandial hypoglycaemia. This is only possible by provision of intravenous Dextrose. Repeated boluses without a maintenance Dextrose infusion are dangerous as they provoke rebound hypoglycaemia due to reactive hyperinsulinaemia. The initial bolus of 3 ml/kg of D10% must be followed by a continuous infusion of D 10% to provide 5-8 mg/kg/min of glucose. Table (5) provides the necessary concentrations and rates of Dextrose infusion which provide such requirement. the majority of stable babies can tolerate 20-30ml/kg/day on top of their daily fluid allowances and thus on day 1 term babies could have 90 ml/kg/day of 10% dextrose while preterm babies <1500 gram could receive 110-120 ml/kg/day of d 10% if required.

In cases where the cardio respiratory status is unstable it is safer to increase the concentration of the infused glucose and keep the fluid at normal allowances or even restricted. Peripheral infusion of concentrations of Dextrose higher than 12.5% must be avoided. An umbilical venous catheter should be used if a percutaneous inserted long line is not available immediately. Strict aseptic techniques must be observed at all times and the position of the umbilical venous catheter or the long line must be verified radiologically as soon as possible. Dextrose concentration of the infused solution should be increased at 2-4 % increments with frequent blood sugar estimation following each change. The increments and weaning should be gradual as described previously.



Babies who are receiving intravenous dextrose infusion due to symptomatic hypoglycaemia must have their blood sugar estimated hourly till three consecutive readings are well above 2.6 mmol/l (46 mg/dl). Thereafter the infused concentration or volume may be decreased according to the clinical judgement and the frequency of blood sugar estimation adjusted accordingly. The algorithm in figure (1) gives a guide towards further management. Blood sugar estimation should continue on regular basis till the infant demonstrate the ability to maintain euglycaemia while on full enteral feeding.

If the requirement for infused glucose exceeds 10-12 mg/kg/min, hyperinsulinaemia is very likely. Table (5) shows the rate of infused glucose per kg/min at various dextrose concentrations. Serum insulin, C-peptide, Cortisol and Growth hormone measurements should be arranged when a concurrent blood sugar is <2.6 mmol/l (< 46 mg/dl). It is at this stage that pharmacological measures to restore glucose haemostasis are to be introduced.

### **5. Pharmacological Interventions**

When the infused glucose at a rate exceeding 10-12mg/kg/minute fails or is just adequate to control the hypoglycaemia, pharmacological interventions are justified. The reader is referred to Table (5) which helps to calculate the infused Glucose per Kg per minute at different Dextrose concentrations and infusion rates. Before any intervention is substituted hyperinsulinaemia should be investigated. Insulin, C-peptide, Cortisol and Growth hormone levels should be obtained when the concurrent level of blood sugar of the infant is at its lowest value. Other endocrine tests may be included after discussion with a metabolic or endocrine centre. An insulin level of > 10 micromol/l in the face of blood sugar < 2.6 mmol/l (<46 mg/dl) is highly suggestive of hyperinsulinaemia which should be ascertained using the criteria described by Aynsley green et al as in table (6) <sup>(19)</sup>. When the

required glucose exceeds a rate of 10-12mg/kg/minute, and while awaiting the results for the metabolic profile, the following suggested pharmacological interventions should be considered:

- Hydrocortisone 5mg/kg intravenously, given 12 hourly should be the first option. In most cases the blood sugar starts to rise within 3-6 hours of the first dose. It is unusual to require hydrocortisone for more than 48 hours and therefore it should be weaned as soon as possible. Recurrence of hypoglycaemia on withdrawal of hydrocortisone indicates an endocrine cause for hypoglycaemia and the necessary cascade of investigations should be set up.
- Diazoxide 5mg/kg 8 hourly should be added if hydrocortisone is ineffectual and a paediatric endocrinologist or a metabolic unit consulted.
- When the combination of hydrocortisone and diazoxide fails to correct the hypoglycaemia, Chlorothiazide 10mg/kg bid should be added.
- Glucagon (100-300 microgram/kg/dose) is not a suitable medication for repeated use in the newborn due to the limited glycogen stores. A single dose which may be repeated once is often successful in maintaining euglycaemia when an intravenous access proved difficult. The effect of a single dose normally last between 1-3 hours. Glucagon is not a substitute to glucose and it should not be used repeatedly.

**NB:** If the results of the investigations point towards persistent hyperinsulinaemia, the referral to an endocrine/ metabolic centre should be promptly initiated. The management of this cohort of babies is complex and may involve surgical intervention.

### **Practical Considerations**

- Early and exclusive breastfeeding is safe to meet the nutritional needs of healthy term newborns worldwide. (20)

- Healthy term newborns who are breastfeeding on demand need not have their blood glucose routinely checked and need no supplementary foods or fluids. (20)
- Healthy term newborns do not develop "symptomatic" hypoglycaemia as a result of simple underfeeding. If an infant develops symptoms ascribed to hypoglycaemia, detailed assessment should be made to ascertain the cause of hypoglycaemia. Management of the cause of hypoglycaemia is as important as the management of hypoglycaemia.(20)
- The maintenance of normal body temperature in addition to breastfeeding is necessary to prevent hypoglycaemia. (20)
- Early feeding should be initiated in all well babies who are at high risk of hypoglycaemia.
- Nasogastric tube feeding and or Intravenous dextrose should not be delayed if the baby is at risk of hypoglycaemia and is clearly not able to establish adequate oral feeding.
- A single dose of Glucagon 100-300 microgram/kg given IM may be used as an emergency measure if delays in securing an intravenous line are anticipated. Regular Glucagon is ineffective and should be avoided.
- The commercial bed side glucometers tend to overestimate the true value of blood sugar at lower values.(21) All values of blood sugars  $< 2.2$  mmol/l ( 40mg/dl) should be confirmed by a proper laboratory test.(21)
- Glucose values should be checked one hour after any intervention addressing the hypoglycaemia.
- Close monitoring of the blood sugar is mandatory till the baby is 12-24 hours on properly spaced enteral feeding.
- Sepsis, metabolic disorders and endocrinopathies should be strongly suspected in cases not responding to dextrose infusions or requiring higher rates of infusion  $> 12$  mg/kg/min to maintain euglycaemia.
- Babies requiring intravenous infusions to correct the hypoglycaemia should be weaned slowly when they are able to tolerate oral feeds.

**Table (1) Causes of Neonatal Hypoglycaemia**

Mechanism	Leading Causes
Decreased Glycogen Stores	Prematurity
	Intrauterine Growth Retardation
	Perinatal Asphyxia
	Starvation
	Glycogen Storage Disorders
Hyperinsulinemia	Infants Of Diabetic Mothers
	Beckwith Wiedemann Syndrome
	Erythroblastosis Foetalis
	Nesidioblastosis
	Maternal Medications
Decreased Glucose Supplies	Exchange Transfusion
	Intrapartum Maternal Dextrose
Mixed Mechanisms ( increased utilisation of glucose, decreased mobilisation of stores etc)	Small For Gestational Age
	Inborn Errors Of Metabolism
Mixed Mechanisms ( increased utilisation of glucose, decreased mobilisation of stores etc)	Hypothermia
	Polycythaemia
	Sepsis
	Adrenal Insufficiency
	Hypopituitarism
	Hypothalamic Disorders
	Maternal Medications

**Table (2) High Risk Screening Groups**

High Risk Babies who should be screened at one hour of age
Premature babies (Gestational age <37 weeks )
Newborns >4.0 kg or <2.0 kg
Large for Gestational Age /LGA (>90th percentile), or Small for Gestational Age /SGA(<10th percentile.)
Infants born to insulin-dependent mothers or mothers with gestational diabetes
Newborns suspected of sepsis or born to mother suspected of having chorioamnionitis
Newborns with symptoms suggestive of hypoglycemia: jitteriness, tachypnoea, hypotonia, poor feeding, apnoea
temperature instability, seizures, lethargy
Significant perinatal asphyxia or five-minute Apgar < 5

**Table (3) Other High Risk Groups**

High Risk Babies to be Screened as Appropriate			
<ul style="list-style-type: none"> <li>• Hypothermic babies( temperature&lt; 36.5 c)</li> <li>• Infant with mother on terbutaline, salbutamol, beta-blockers, or oral hypoglycemic agents.</li> <li>• Infant with isolated hepatomegaly (rule out glycogen storage disease [GSD]).</li> <li>• Polycythaemic babies (PCV &gt;65%)</li> <li>• Dysmorphic babies or babies with microcephaly or anterior midline defects.</li> <li>• Infants with macroglossia or hemihypertrophy (Beckwith-Wiedemann Syndrome)</li> <li>• Infants with suspected an inborn error of metabolism.</li> </ul>			
<ul style="list-style-type: none"> <li>• Babies undergoing exchange transfusion.</li> </ul>			

TO MAKE	ADD THIS AMOUNT OF GLUCOSE IN mls %50	TO THIS MOUNT OF A %10DEXTROSE in mls	TOTAL BAG IN mls
%12D	25	475	500
%14D	50	450	500
%18D	100	400	500
%22D	150	350	500
% 26D	200	300	500

**Table (4) Preparations of Various Dextrose Concentrations**

**Table (5) Glucose Rate Calculator**

INFUSION RATE DAY/KG/ML	.Dex %10	.Dex %12	.Dex %14	.Dex %18
60	4.2	5.0	5.8	7.5
90	6.25	7.5	8.75	11.3
120	8.3	10.0	11.7	15
150	10.4	12.5	14.6	18.8
180	12.5	15.0	17.5	22.5

Infusion Rate of Glucose mg/Kg/min

**Table 6. Diagnostic criteria for hyperinsulinism**

- Glucose requirement > 6-8mg/kg/min to maintain blood glucose above 2.6-3mmol/litre
- Laboratory blood glucose <2.6 mmol/litre.
- Detectable insulin at the point of hypoglycaemia with raised C peptide.
- Inappropriately low blood free fatty acid and ketone body concentrations at the time of hypoglycaemia
- Glycaemic response after the administration of glucagons when hypoglycaemic.
- Absence of ketonuria.

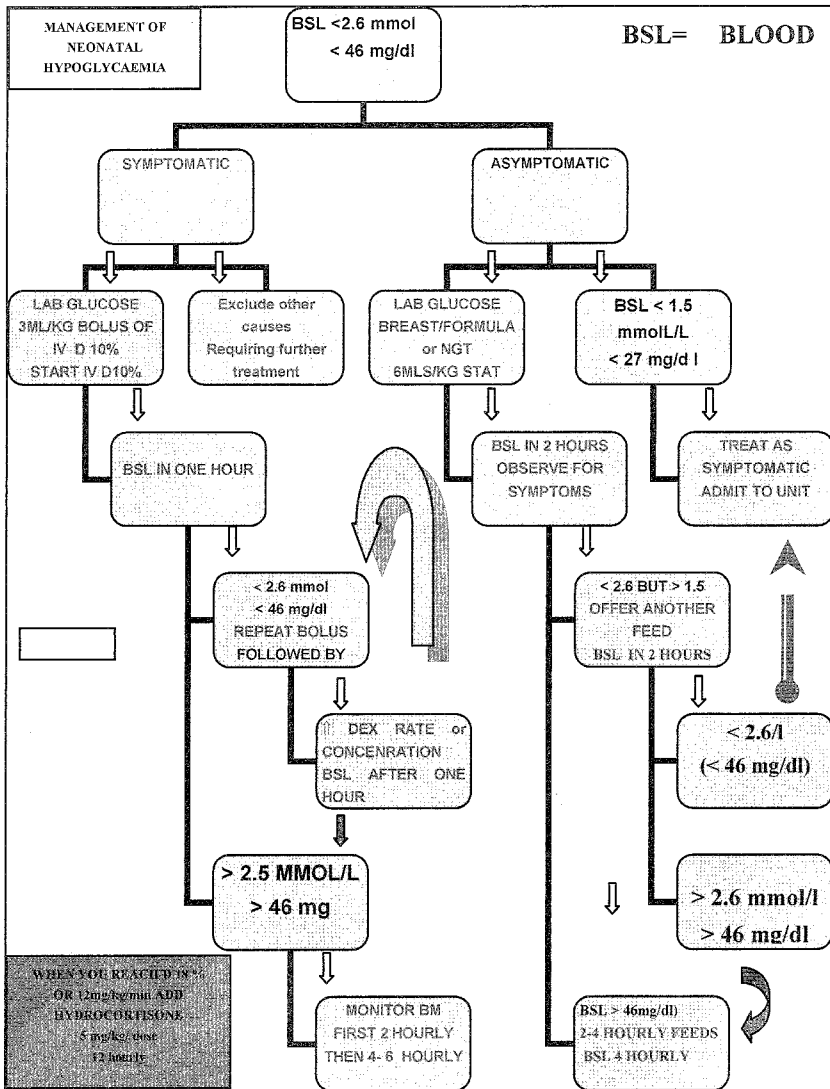


Fig (1) Glycaemic response after the administration of Glucagon when hypoglycaemic Absence of ketonuria Adopted from (A Aynsley-Green et al. Practical management of hyperinsulinism in infancy Arch. Dis. Child. Fetal Neonatal Ed., Mar 2000; 82: 98 – 107)

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