Guideline

# Hyperglycaemia: Management of Preterm Infants in Neonatal Intensive Care

## 1. Purpose

Hyperglycaemia in preterm infants is likely due to a number of factors (impaired insulin secretion, insulin resistance and immaturity of glucose homeostasis regulation)[1,2.] Hyperglycaemia has been associated with increased mortality and morbidity in preterm infants (including IVH, NEC, infection and retinopathy of prematurity)[3-5.]

Studies in adults suggest that using insulin to control hyperglycaemia in critically ill patients is associated with increased survival and decreased rates of sepsis[6]. However, it is not yet clear whether insulin use improves significant outcome in preterm infants. Evidence supporting various management strategies is also poor. Despite this, the use of insulin to manage hyperglycaemia in preterm infants has become routine practice in ANZNN units[7].

Given the lack of evidence to guide effective use, this guideline aims to highlight issues to consider when hyperglycaemia occurs in preterm neonates and to promote consistency of approach in management.

## 2. Definitions

**Hyperglycaemia:** True Blood Glucose (TBG) >10-12mmol/L

There is continued uncertainty as to what constitutes a level of hyperglycaemia that is likely to result in an adverse outcome and thus justifies specific intervention[7]. It is unusual to see TBG levels above 7mmol/L in healthy term infants, thus many authors have defined levels above 8mmol/L as hyperglycaemia[3,8], with intervention suggested at various thresholds, often around 10-12mmol/L.

## 3. Responsibilities

Staff caring for preterm infants with hyperglycaemia in Neonatal Intensive Care should follow this guideline.

## 4. Guideline

### *4.1 Indication for initiating intervention:*

- TBG >12mmol/L for more than 6 -12 hours.

This is an arbitrary definition of significant hyperglycaemia as TBGs in preterm infants can vary significantly over time, particularly in the first week of life[9].

It may be reasonable to continue current management over a longer period than 12 hours if TBG <15mmol/L and the infant is otherwise stable (discuss with consultant).

### *4.2 Management*

Management options include the following:

#### Reduce glucose intake

If infused glucose levels are high (>8-10mg/kg/min), reduction of glucose intake alone may be sufficient to decrease TBG to an acceptable level.

The process includes the following:

- change infusion solutions containing 10% glucose to normal or half normal saline (if compatible) before decreasing total fluid intake or stopping parental nutrition
- do not reduce glucose intake below 5-6mmol/kg/min (80ml/kg/day of 10% glucose or PN = 5.6mg/kg/min) as this is the minimum required to maintain adequate caloric intake
- do not reduce total fluid intake below that required to maintain hydration
- document glucose infusion rate on daily fluid chart for all infants with hyperglycaemia
- count insulin infusion in daily total fluid intake.

$$\text{Glucose infusion rate (mg/kg/min)} = \frac{\%\text{glucose X mL/kg/day}}{144} = \frac{\%\text{glucose X mL/h}}{6 \text{ X body wgt (kg)}}$$

Breast milk/standard formula is approx 7% carbohydrate, LBW formula approx 8%, FEBM 10%.

Resource: online calculator (access via the following website): www.nicutools.org.

Glycosuria alone should not initiate reduction of glucose intake in the absence of significant hyperglycaemia as osmotic diuresis and subsequent dehydration is unlikely if TBG<12mmol/L[10].

### Insulin Infusion

Aim to normalise blood glucose levels (TBG to 4-10mmol/L) whilst avoiding hypoglycaemia by considering the following:

- insulin infusion - starting dose: 0.05 units/kg/hour – mid range dose
- adjust insulin rate gently (i.e. steps of 0.01-0.02 units/kg/hour) with sufficient time between adjustments to monitor effects (approx 4 hours)
- If feeds are stopped, or fluids changed, re-calculate glucose intake. Small adjustments of infusion and more frequent TBG monitoring may be required
- If TBG drops sharply or HYPOglycaemia (TBG <2.6mmol/L) occurs, decrease insulin rate (e.g. halve it), rather than stopping completely. Repeat TBG at more frequent intervals until stable (e.g. hourly)
- If severe HYPOglycaemia (TBG <1.5mmol/L), stop insulin infusion, give bolus of 2ml/Kg of 10% glucose. Rarely glucagon may be considered if there is no response (discuss with consultant).

Maintenance infusion rate is likely to be less than that required to decrease TBG level.

Some infants are very sensitive to rapid changes in infusion rates with unpredictable responses, thus care is needed when increasing infusion rates.

## *4.3 Monitoring*

Timing of TBGs:

- use the NISC Blood Gas Analyser to measure TBG
- test one hour after starting infusion (note: some infants are sensitive to insulin and their TBGs drop quickly with the introduction of insulin)
- once stabilised, TBG can be tested 4-6 hrly
- check blood sugar levels more frequently if:
    - rate of administration of infused insulin and/or maintenance glucose / feed is changed
    - medication mixed with glucose and/or an insulin infusion is disrupted
    - new infusion mix is commenced.

Use of blood glucose monitor and reagent strips to minimise test blood volume is acceptable for infants with hyperglycaemia who are having frequent samples taken if TBGs are stable above 4mmol/L. All reagent strip levels <4mmol/L should be confirmed with TBG.

## *4.4 Other information*

### Variability of insulin infusate

The insulin concentration in the infusion as it enters the infant may increase over time as binding sites become saturated because insulin binds to plastic syringes and lines[11,12]. The method of flushing and sitting lines is designed to promote saturation of binding sites and thus improve stability of the solution. Regular TBG monitoring also assists in preventing hypoglycaemia, which is potentially more likely toward the end of a 24 hour period as saturation occurs and infusate concentration increases.

For more information regarding insulin infusion, refer to IV medication manual: **Insulin protocol**.

### Sepsis

Sepsis is commonly associated with hyperglycaemia, therefore when hyperglycaemia occurs, infection should be actively sought and treated as indicated.

### Persistent Hyperglycaemia

Hyperglycaemia in preterm infants tends to be a transitory phenomenon and insulin treatment can be stopped after a few days. If hyperglycaemia persists more than 2 weeks, consider alternative diagnoses such as neonatal diabetes (1:400,000); investigations include serum insulin, C-peptide and ketones and urine ketones8. Consult an Endocrinologist after discussion with neonatal consultant.

## 5. Evaluation, monitoring and reporting of compliance to this guideline

Compliance to this guideline will be monitored via clinical incident reported through Victorian Health Incident Management System (VHIMS).

## 6. References

Online calculator (access via the following website): www.nicutools.org.

Evidence table: Hyperglycaemia: Management of Preterm Infants in Neonatal Intensive Care

## 7. Legislation/Regulations related to this guideline

Not applicable.

## 8. Appendices

Appendix 1: Evidence Table: Hyperglycaemia: Management of Preterm Infants in Neonatal Intensive Care.

**Appendix 1**

# Evidence Table – Hyperglycaemia: Management of Preterm Infants in Neonatal Intensive Care

| Author/s | Title | Source | Level of Evidence (1-1V) | Comments |
|---|---|---|---|---|
| 1. Mericq V. | Prematurity and insulin sensitivity. | Hormone Research 2006;65 Suppl 3:131-6. | III-3 | review |
| 2. Mitanchez-Mokhtari D, Lahlou N, Kieffer F, Magny JF, Roger M, Voyer M. | Both relative insulin resistance and defective islet beta-cell processing of proinsulin are responsible for transient hyperglycemia in extremely preterm infants. | Pediatrics 2004;113:537-41. | III-2 | Prospective comparative |
| 3. Hall NJ, Peters M, Eaton S, Pierro A. | Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis. | Journal of Pediatric Surgery 2004;39:898-901; | III-2 | cohort |
| 4. Hays SP, Smith EOB, Sunehag AL. | Hyperglycemia Is a Risk Factor for Early Death and Morbidity in Extremely Low Birth-Weight Infants. | Pediatrics 2006;118:1811-8. | III-2 | cohort |
| 5. Manzoni P, Castagnola E, Mostert M, Sala U, Galletto P, Gomirato G. | Hyperglycaemia as a possible marker of invasive fungal infection in preterm neonates. | Acta Paediatrica 2006;95:486-93. | III-2 | Case control |
| 6. Van den Berghe G, Wouters PJ, Bouillon R, et al. | Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. | Crit Care Med 2003;31:359-66. | II | Prospective randomised |
| 7. Alsweiler JM, Kuschel CA, Bloomfield FH. | Survey of the management of neonatal hyperglycaemia in Australasia. | Journal of Paediatrics and Child Health 2007;43:632-5. | | survey |
| 8. Ogilvy-Stuart AL, Midgley P. | Practical Neonatal Endocrinology | Cambridge University Press; 2006. | | text |
| 9. Hey E. | Hyperglycaemia and the very preterm baby | Seminars in Fetal and Neonatal Medicine 2005;10:377-87. | III-2 | cohort |
| 10. Coulthard MG, Hey EN | Renal processing of glucose in well and sick neonates. | Archives of Disease in Childhood Fetal & Neonatal Edition 1999;81:F92-8. | III-2 | cohort |
| 11. Hewson M, Nawadra V, Oliver J, Odgers C, Plummer J, Simmer K. | Insulin infusions in the neonatal unit: delivery variation due to adsorption. | Journal of Paediatrics & Child Health 2000;36:216-20. | | In-vitro |
| 12. Fuloria M, Friedberg MA, DuRant RH, Aschner JL. | Effect of Flow Rate and Insulin Priming on the Recovery of Insulin From Microbore Infusion Tubing. | Pediatrics 1998;102:1401-6. | | In-vitro |