Recommendations- Diagnosis

Question 11. What are the benefits and risks of testing?

PICO: Should testing for neonatal hypoglycaemia vs. not testing be used for babies at risk of neonatal hypoglycaemia?

Recommendation 11:

Blood glucose measurements should be offered for babies with identified risk factors of neonatal hypoglycaemia (see recommendation 12). [Conditional recommendation]

Justification: Most babies with hypoglycaemia have no clinical signs, so blood testing is the only way to detect low glucose concentrations.

It is common practice to test babies considered at risk of neonatal hypoglycaemia and there is no evidence to support changing this approach.

There is no robust evidence of benefit for at-risk babies and some evidence of harm, primarily from painful procedures and a reduction in breastfeeding. Nevertheless, the potential for death and brain damage from undiagnosed hypoglycaemia was considered to outweigh the pain and distress caused by testing.

Although resource requirements are substantial, with current screening criteria applicable to 26-28% of all babies, it is feasible as it is currently being done.

Implementation considerations: Whānau should be fully informed about the reasons for testing and encouraged to participate in decisions about pain relief (see recommendation 13). Provide easily understandable information in a range of formats, including videos and apps. Address how babies can be supported during tests, and how the test can be made less painful for the baby (see recommendation 14).

Monitoring and evaluation: Nil.

Research priorities:

Studies are needed on:

Outcomes in children whose whānau declined screening for neonatal hypoglycaemia and the reasons for declining.

Health Equity: Screening rates for babies delivered rurally or from underrepresented groups are not known. However, if testing is implemented equitably, this is likely to increase health

equity. Ask whānau what their preferences are for painful procedures. Some whānau may wish to use rongoā Māori (traditional Māori medicine that takes a holistic approach) e.g. waiata, karakia, oriori to support pēpi during a painful procedure.

Evidence to decision table: refer to Appendix G

Question 12. Who to test?

i) Which babies are at increased risk of neonatal hypoglycaemia?

ii) Which babies should be tested for neonatal hypoglycaemia?

iii) Which signs and symptoms are indications for testing?

PICO: Should expanded or restricted criteria vs. current criteria be used for screening for neonatal hypoglycaemia?

Recommendation 12:

Screening is recommended for babies with the following risk factors:

- Maternal diabetes (any type);
- Preterm birth (<37 weeks' gestation);
- Small for gestational age (<10th percentile using customised or population growth charts);
- Large for gestational age (>90th percentile using customised or population growth charts);
- If gestation unknown: low birthweight (<2500 g) or macrosomia (>4500 g);
- Unwell (e.g. respiratory distress, history of fetal distress or asphyxia, hypothermia, delayed or poor feeding);
- Maternal use of antidepressant medications, alpha or beta blocker medications, amphetamines (both prescribed and not prescribed), anti-psychotic medications.

Screening is recommended for babies with any clinical signs potentially related to hypoglycaemia including: jitteriness, seizures, poor feeding, lethargy, irritability, cyanosis, hypotonia, apnoea, tachypnoea, hypothermia, respiratory distress, asphyxia, abnormal cry, pallor, and vomiting. **[Conditional recommendation]**

Justification: These criteria are similar to those already in use around Aotearoa New Zealand.

The cost of testing is likely to be small compared to the cost of brain injury from undetected hypoglycaemia for the individual, although the evidence that prompt detection and treatment of hypoglycaemia alters neurodevelopmental outcomes is very uncertain.

Implementation considerations:

Testing should be undertaken using a reliable analyser (see recommendation 14).

Address how babies can be supported during tests, and how the test can be made less painful for the baby (see recommendation 13).

A full assessment, including clinical history, should be made for babies exhibing any signs of neonatal hypoglycaemia. Consider prompt referral to a paediatrician if a baby is unwell or shows clinical signs associated with neonatal hypoglycaemia. However, testing and treatment if required should not be delayed pending such referral (see recommendation 21).

The Small for Gestational Age / Fetal Growth Restriction Guidelines of Aotearoa New Zealand recommend using customised centiles to define small for gestational age (1).

Monitoring and evaluation: Nil

Research priorities:

Studies are needed on:

Outcomes of screening versus not screening large-for-gestational age babies.

Health Equity: The frequency of risk factors for hypoglycaemia varies with ethnicity. Ensure whānau are fully informed of the reasons for testing, health benefits and potential adverse effects of blood glucose testing, and the results of any tests. Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question 13. When to test?

i) At what age should testing start?

ii) How often should testing be performed?

iii) When should testing stop?

PICO: Should other timings vs. start at 1-2 hours, intervals of 3-4 hours, finish after 12 hours of glucose concentrations above the threshold be used for testing neonatal hypoglycaemia?

Recommendation 13:

Test the blood glucose concentration of babies at risk of neonatal hypoglycaemia at 1-2 hours after birth, (preferably after the first feed but before 2 hours) then at intervals of 3-4 hours, independent of feeding schedule. [**Conditional recommendation**]

Stop testing after glucose concentrations have remained ≥2.6 mmol/L for 12 hours from birth or from the first normal test (≥2.6 mmol/L) after any low glucose concentrations (<2.6 mmol/L) provided the baby is feeding adequately.

Justification: There is a physiological nadir in blood glucose concentrations at approximately 30-90 minutes after birth. In many babies, low glucose concentrations during this period will resolve spontaneously. Limited evidence suggests that low glucose concentrations are more common at 1 hour than at 2 hours and become less common thereafter.

A relatively small proportion (0.3-1.1%) of cases of neonatal hypoglycaemia may be missed if screening ends at 12 hours.

Severe hypoglycaemia is most common within the first 12 hours after birth.

Limited evidence suggests that 10 – 17% of episodes occur between the initial test at 1–2 hours and the second test, approximately 3–4 hours later, so repeated testing is required.

There is very little change in blood glucose concentrations with feeding in the first 48 hours, so timing of testing can be independent of feeding.

Implementation considerations: The criteria for stopping testing should be 12 hours of blood glucose concentrations ≥2.6 mmol/L with adequate feeding, not the number of tests conducted.

Monitoring and evaluation: Babies who have required intravenous dextrose or supplemental feeds for the treatment of neonatal hypoglycaemia should have 12 hours of blood glucose concentrations ≥2.6 mmol/L after these additional measures have ended before testing is stopped.

Research priorities: The correct time to stop testing is not known. The GLOW study showed that healthy term babies continued to have episodes of glucose concentrations <2.6 mmol/L up to 5 days after birth, although few occurred after 3 days.

Studies are needed on:

1. whether extending screening beyond 12 hours improves outcomes.
2. the frequency and clinical significance of glucose concentrations <2.6 mmol/L after 12 hours in babies who previously had glucose concentrations ≥2.6 mmol/L.

Health Equity: Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question14. What is the best care for babies while being tested?

PICO: Should specific pain management strategies vs. control/ placebo/ no intervention be used for pain management during blood sampling for neonatal hypoglycaemia?

Recommendation 14:

Pain management strategies should be used during blood sampling for neonatal hypoglycaemia. [Conditional recommendation]

Effective pain management strategies include skin-to-skin contact, breastfeeding, and oral sucrose.

Justification: Skin-to-skin contact, breastfeeding, and oral sucrose each result in medium to large reductions in pain scores related to heel-prick testing with minimal or no apparent adverse effects. Expressed breastmilk may also result in a small reduction in pain scores but there are few studies and the evidence is very uncertain.

Implementation considerations: Whānau should be given the opportunity to be involved in the choice of and provision of pain management related to blood testing.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Ask whānau what their preferences are for painful procedures. Some whānau Māori may wish to use rongoā Māori (traditional Māori medicine that takes a holistic approach) e.g. waiata, karakia, oriori to support pēpi during a painful procedure.

Evidence to decision table: refer to Appendix G

Question 15. Which type of device should be used for testing?

PICO: Should a point-of-care testing method be used to screen for hypoglycaemia in neonates?

Recommendation 15:

Testing should use a validated and reliable point-of-care device using a glucose oxidase, glucose dehydrogenase or hexokinase method with electrochemical or amperometric detection. [Strong recommendation]

Justification: Using more reliable testing methods is essential for accurate diagnosis and treatment. It can also reduce the number of heel pricks and is cost saving.

The common practice of using a less accurate device, with confirmation of low glucose concentrations using a more accurate device, is NOT appropriate as it does not address the problem of false negative tests (13-30%), potentially delays treatment, and increases costs.

The panel considered that recommending more reliable devices was essential to drive improvements in equity and resource allocation, leading to long-term cost savings despite potentially initial higher costs.

Implementation considerations: Examples of currently available devices meeting these requirements include Elite XL, iSTAT, Freestyle, and ABL 800.

Monitoring and evaluation: A list of currently available devices that are appropriate for neonatal blood glucose testing should be made widely available and updated regularly.

Research priorities: Nil.

Health Equity: It is essential that appropriate analysers are available in all settings where newborn babies are cared for, including in primary units, to avoid potentially widening health inequities.

Evidence to decision table: refer to Appendix G

Question 16. What is the best working definition (operational threshold) of neonatal hypoglycaemia?

PICO: Should higher or lower blood glucose concentrations vs. blood glucose concentration of 2.6 mmol/L be used for defining of neonatal hypoglycaemia?

Recommendation 16:

A blood glucose concentration of <2.6 mmol/L should be used as the definition (operational threshold) for neonatal hypoglycaemia. [Conditional recommendation]

Justification: There is some evidence for supporting the current operational threshold of <2.6mmol/L, and a lack of evidence to justify changing it.

Low certainty evidence from a single RCT shows that using a threshold of <2.0mmol/L has little to no effect on neurodevelopmental outcomes at 18 months but results in a large increase in moderate hypoglycaemia (2.0 – 2.6 mmol/L), and a moderate increase in severe hypoglycaemia (<2.0 mmol/L). The effect on serious adverse effects was uncertain.The

panel noted that babies with initial blood glucose concentrations <1.9 mmol/L were excluded from this trial, and that 18 months was likely too early to detect any effects of hypoglycaemia on neurodevelopmental outcomes of interest.

The operational threshold of blood glucose concentrations <2.6 mmol/L is consistent with WHO guidelines (2).

Implementation considerations: Consider additional investigations (see recommendation 18) and consultation with an paediatric endocrinologist or other relevant specialist if hypoglycaemia persists after 72 hours of age.

Monitoring and evaluation: Blood glucose concentrations should continue to be monitored while babies are being treated for hypoglycaemia and for at least 12 hours after treatment stops and baby is feeding adequately.

Research priorities:

Studies are needed on:

Benefits and harm of changing to a lower or higher glucose threshold, particularly on later neurodevelopmental outcomes at least through to school age.

Health Equity: The impact on health equity is not clear.

Evidence to decision table: refer to Appendix G

Question 17. What clinical observations are needed?

PICO: Should clinical observations vs. other/no clinical observations be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 17:

Clinical observations are recommended for monitoring all babies at risk of or with neonatal hypoglycaemia. [Conditional recommendation]

All newborn babies require clinical observation in the first hours and days after birth. Any signs that are associated with neonatal hypoglycaemia should result in prompt measurement of blood glucose concentrations (see recommendation 11).

Justification: Clear evidence supports the benefits of monitoring, as babies showing clinical signs of hypoglycaemia tend to have poorer outcomes than those who do not.

Some babies who develop severe and potentially brain-threatening hypoglycaemia do not have risk factors or have a recurrence of hypoglycaemia after hospital discharge. These babies will only be identified by clinical signs.

Implementation considerations: It is important to educate whānau of all babies about clinical signs that may indicate hypoglycaemia and how to seek help if these occur. This includes at-risk babies who have normal blood glucose concentrations in the first 12 hours and those whose hypoglycaemia appears to have resolved.

Monitoring and evaluation: Nil.

Research priorities

Studies are needed on:

Optimal protocols for clinical observations in babies at risk of hypoglycaemia, including the best predictors of hypoglycaemia and duration of monitoring.

Health Equity: Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question 18. What is the role of interstitial or transcutaneous glucose measurement?

PICO: Should continuous glucose monitoring vs. intermittent blood glucose testing be used for babies at risk of or diagnosed with neonatal hypoglycaemia?

Recommendation 18:

Continuous glucose monitoring should not be used *routinely* for the diagnosis and monitoring of neonatal hypoglycaemia. [Conditional recommendation]

Justification: In two RCTs in VLBW babies, those with continuous glucose monitoring (CGM) spent more time with blood glucose concentrations in the normal range and underwent fewer blood tests. However, there was little to no effect on the number of hypoglycaemia events.

Current devices are not sufficiently accurate for use in babies (approximately ±1 mmol/L accuracy) and technical difficulties can be time consuming to remedy.

CGM is well tolerated in babies, and insertion may be less painful than heel-prick blood tests.

CGM is cost-effective in adults with diabetes, but its cost-effectiveness in babies is uncertain.

Implementation considerations: Nil.

Monitoring and evaluation: This technology is evolving rapidly, so this recommendation should be reviewed frequently.

Research priorities:

Studies are needed on:

1. The potential utility of CGM when a baby is transitioning from intravenous dextrose to breastfeeding.
2. The utility of CGM in late preterm and term babies at risk of hypoglycaemia.
3. The clinical significance of episodes of low glucose concentrations that would not have been detected without CGM, including their association with neurodevelopmental outcomes, and the effect of treatment on these outcomes.
4. The cost-effectiveness of using CGM in babies whose glucose concentrations are very unstable.
5. Whānau perspectives on use of CGM in babies.

Health Equity: The effect on health equity is not known but is likely to depend on access to the devices and the specialist expertise required to use them. Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question 19. Should metabolites other than glucose be measured?

PICO: Should measurement of other metabolites in addition to glucose vs. measurement of glucose alone be used for diagnosing and monitoring of neonatal hypoglycaemia?

Recommendation 19:

Ketones, lactate, and insulin concentrations should not be measured *routinely* in addition to glucose for the diagnosis and monitoring of neonatal hypoglycaemia in the first 72 hours. [Conditional recommendation]

Consider measuring glucose, beta-hydroxybutyrate, and insulin concentrations in babies with hypoglycaemia that persists beyond 72 hours to help distinguish between those with congenital hyperinsulinemia and those with other causes.

Justification: Measuring ketones, lactate or insulin may help uncover uncommon causes of hypoglycaemia but requires additional blood tests, thus causing additional distress to the baby and whānau and incurring additional costs.

Since most neonatal hypoglycaemia is transitional, testing before 72 hours may show concerning findings (e.g. detectable insulin concentrations at the time of low glucose concentrations) that will resolve spontaneously and therefore should not alter management for most babies.

Preliminary evidence suggests that measuring ketones at approximately 72 hours may help distinguish the cause of the hypoglycaemia (3).

If hyperinsulinism is suspected and there are no risk factors for hypoglycaemia, insulin concentrations might be measured earlier. However, there was uncertainty about whether testing before 72 hours makes a difference even for congenital hyperinsulinism.

The overall consensus was that 72 hours is an appropriate time to consider measuring other metabolites, as testing earlier is unlikely to be useful.

Implementation considerations: Consider measuring insulin before 72 hours if hypoglycaemia is severe (<1.5 mmol/L) and the baby does not have risk factors for hypoglycaemia or has other concerning clinical features. Additionally, consider paediatric endocrinology/metabolic referral for severe hypoglycaemia (<1.5 mmol/L) within the first 72 hours.

Monitoring and evaluation: Nil

Research priorities: Nil

Health Equity: The additional blood tests may not be available at all healthcare facilities, which could potentially worsen inequities for those with limited access. However, it is possible to collect the samples at any facility and have them analysed at a different location, helping to reduce some of the access barriers.

Evidence to decision table: refer to Appendix G

Question 20. What neurological monitoring/ imaging is needed?

PICO: Should neurological monitoring/ imaging vs. no neurological monitoring/ imaging be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 20:

Neurological monitoring and brain imaging should not be used *routinely* for monitoring babies with neonatal hypoglycaemia. [Conditional recommendation]

Consider using early MRI (within 6 days of onset of hypoglycaemia) for babies with severe (<1.0 mmol/L) or persistent hypoglycaemia to assist with counselling and prognosis.

Justification: Early MRI findings, particularly diffusion-weighted imaging, are moderately predictive of later neurodevelopmental outcomes after neonatal hypoglycaemia. This may be helpful in some cases, e.g. for counselling whānau, guiding management decisions, supporting Accident Compensation Commission claims and access to early neurodevelopmental therapy to optimise outcomes.

One study found that changes in cotside aEEG were not clinically useful for monitoring brain function in relation to neonatal hypoglycaemia.

Implementation considerations: Timely access to MRI can be challenging due to the high cost and limited availability. It is important to discuss this decision with a neonatologist, as this may involve transfer to a secondary or tertiary centre.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Health equity may be increased if all whānau are offered access to MRI and are appropriately informed about the risks and benefits.

Evidence to decision table: refer to Appendix G

References:

1. Te Whatu Ora – Health New Zealand. Small for gestational age and fetal growth restriction in Aotearoa New Zealand He Aratohu Ritenga Haumanu mō te Tōhuatanga Kōpiri me te Pakupaku Rawa. A clinical practice guideline: Summary of recommendations. Wellington: Te Whatu Ora – Health New Zealand; 2023 [cited 2024 December 18]. Available from: https://www.tewhatuora.govt.nz/publications/small-for-gestational-age-fetal-growth-restriction-guidelines

2. World Health Organization (WHO). Guidelines for the management of neonatal hypoglycemia 2019 [cited 2024 March 14]. Available from: https://platform.who.int/docs/default-source/mca-documents/policy-documents/operational-guidance/ARE-MN-62-01-OPERATIONALGUIDANCE-2015-eng-Neonatal-Hypoglycemia-Guideline.pdf

3. Stanley CA, Weston PJ, Harris DL, De Leon DD, Harding JE. Role of beta-hydroxybutyrate measurement in the evaluation of plasma glucose concentrations in newborn infants. Archives of disease in childhood Fetal and neonatal edition. 2024;109(6):580-5.