EtD 7. Should Insulin vs. glucose reduction be used for hyperglycaemic preterm infants?

POPULATION:	Hyperglycaemic preterm infants
INTERVENTION:	Insulin
COMPARISON:	Glucose infusion reduction
MAIN OUTCOMES:	**Critical for making a decision** Mortality Neurodevelopmental impairment Adverse effects **Important but not critical** Fully breastfeeding at hospital discharge Faltering growth/body composition Duration of initial hospital stay Time to full enteral feeds Bronchopulmonary dysplasia Necrotising enterocolitis (NEC) Sepsis: proven or suspected Retinopathy of prematurity Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Of limited importance** Fully breastmilk feeding at hospital discharge Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation - patient perspective
BACKGROUND:	Hyperglycaemia is a frequent metabolic complication in preterm infants, particularly those born extremely preterm or with very low birthweight. It often arises due to the immaturity of glucose homeostasis, stress-related hyperglycaemia, or the administration of glucose-containing fluids. Hyperglycaemia has been linked to an increased risk of complications, including intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis, sepsis, prolonged hospitalisation, and increased mortality. Managing hyperglycaemia in preterm infants typically involves reducing glucose infusion rates (GIR) or administering insulin. Reducing GIR lowers exogenous glucose delivery but may increase the risk of hypoglycaemia and reduced caloric intake, potentially impairing growth and neurodevelopment. Reducing the glucose infusion rate alone may not be enough to achieve glycaemic control. Prolonged reductions in glucose load can lead to energy deficits, which may negatively affect somatic growth, including weight gain, length and head circumference growth. Conversely, insulin therapy improves glucose utilisation and may maintain energy balance, but it carries risks such as hypoglycaemia, electrolyte imbalances, and the need for close monitoring to avoid adverse outcomes. Evidence on the optimal management strategy for hyperglycaemia in preterm infants remains inconclusive. While some studies suggest that insulin therapy may improve growth outcomes, it also increases the risk of hypoglycaemia, raising concerns about its safety. Reducing glucose load is a more straightforward intervention. Still, it may compromise nutrition especially in infants

	reliant on intravenous nutrition.
CONFLICT OF INTERESTS:	The following systematic review on Guidelines (Meliana M, et al) co-authors are on the Guideline Development Group: Barbara Cormack, Tanith Alexander, Luling Lin and Frank Bloomfield and supervised the first author.

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Evidence from two randomised trials of ELBW infants from the 1990's [1,2]. Neither of the studies investigated long-term outcomes, and both had very short-term outcomes in hospitals. **Mortality:** RCT: Little or no evidence of a difference in mortality between insulin and glucose reduction [Critical]. **Adverse effects:** RCT: Insulin-treated infants tolerated significantly higher glucose infusion rates (20.1 ± 2.5 vs. 13.2 ± 3.2 mg/kg/min; p<0.01). No difference between insulin vs. glucose reduction for hypoglycaemia (1% vs. 0%) [Critical]. **No faltering growth/body composition:** RCT: Weight gain was higher in the insulin-treated group (20.1 ± 12.1 vs. 7.8 ± 5.1 g/kg/day; p<0.01). No change in the fractional increase in length (0.05 +/- 0.04 vs. 0.05 +/- 0.05 [units of measurement not specified]) or head circumference (head circumference (0.17 +/- 0.06 vs. 0.19 +/- 0.05 [units of measurement not specified])[Important]. **Time to full enteral feeds:** RCT: Days to reach 60 kcal/kg/day was significantly lower in the insulin group compared with control (5.5 days +/- 0.6 vs. 8.6 days +/- 1.3), p <0.01). **Bronchopulmonary dysplasia (BPD) / chronic lung disease:** RCT: Little or no difference between insulin and control group (77% vs. 66%). [Important] **Sepsis:** RCT: Incidence of sepsis was lower in the insulin versus glucose reduction group (5 vs. 9 events, p<0.05). [Important] **Desirable effects for Māori** No additional evidence available	USA: RCT [1] ELBW infants. Minimum glucose intake was not defined, and the insulin rate was 0.04 U/hr, adjusted to maintain serum glucose between 5.5–9.9 mmol/L. USA: RCT [2] ELBW infants. Minimum glucose intake of 5 mg/kg/min, and the insulin rate was a minimum dose of 0.01 IU/kg/h to a max of 1.0 U/kg/h to maintain blood sugar levels between 4.4–8.9 mmol/L. Minimal glucose recommendations are usually based on the endogenous glucose production rate and the glucose oxidation capacity. The estimated glucose production and glucose oxidation rates in preterm infants are ~6 mg/kg/min (8.6 g/kg/d) and ~8 mg/kg/min (11.5 g/kg/d), respectively [3-5]. **Additional information** In a systematic review of international neonatal nutrition guidelines [6] which assessed carbohydrate recommendations. "Seven guidelines recommended a wide range of parenteral carbohydrate intake from 4 to 17 g/kg/day (2.8 to 11.8 mg/kg/min) in the first week and 11–17 g/kg/day (7.6 to 11.8 mg/kg/min) thereafter.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with glucose reduction	Risk difference with Insulin
Mortality	24	⨁◯◯◯	-	No difference in outcomes between insulin vs. glucose reduction for	

	(1 RCT)	Very low[a,b,c,]		mortality n=3 vs. n=2.	
Neurodevelopmental impairment - not measured	-	-	-	-	-
Adverse effects: RCT assessed with: Tolerated higher glucose infusion rates	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	Insulin-treated infants tolerated significantly higher glucose infusion rates (20.1 ± 2.5 vs. 13.2 ± 3.2 mg/kg/min; p<0.01).	
Adverse effects: RCT assessed with: Hypoglycaemia	24 (1 RCT)	⨁◯◯◯ Very low[a,b,c,]	-	No difference in outcomes between insulin vs. glucose reduction for hypoglycaemia (1% vs. 0%).	
Fully breastfeeding at hospital discharge - not measured	-	-	-	-	-
Faltering growth / body composition: RCT assessed with: Weight gain (g/kg/day)	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	Weight gain was significantly higher in the insulin group (20.1 ± 12.1 vs. 7.8 ± 5.1 g/kg/day; p<0.01). Weight was significantly greater in insulin-treated infants from study day 4 through 14 (p <0.05). The insulin-treated infants had a significantly greater fractional increase over baseline weight at the end of the study (0.24 ± 0.14 vs. 0.12 ± 0.10; p <0.05).	
Faltering growth / body composition: RCT assessed with: Length (measurement not specified)	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	No change in the fractional increase in length (0.05 +/- 0.04 vs. 0.05 +/- 0.05).	
Faltering growth / body composition: RCT assessed with: Head circumference (measurement not specified)	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	No change in the fractional increase in head circumference (0.17 +/- 0.06 vs. 0.19 +/- 0.05).	
Duration of initial hospital stay - not measured	-	-	-	-	-
Time to full enteral feeds	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d]	-	Days to reach 60 kcal/kg/day was significantly lower in the insulin group compared with control (5.5 +/- 0.6 vs. 8.6 +/- 1.3; p < 0.01).	
Bronchopulmonary dysplasia (BPD) / chronic lung disease	56 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	No difference in outcomes between insulin vs. glucose reduction for bronchopulmonary dysplasia (77% vs. 66%).	
Necrotising enterocolitis (NEC) - not measured	-	-	-	-	-
Sepsis: proven or suspected: RCT	24 (1 RCT)	⨁◯◯◯ Very low[a,b,d,]	-	Incidence of sepsis was lower in the insulin vs. glucose reduction group (5 vs. 9, p<0.05).	
Retinopathy of prematurity (ROP) - not measured	-	-	-	-	-
Anaemia of prematurity - not measured	-	-	-	-	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Fully breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-

a. Downgraded one level due to concerns of risk of bias
b. Downgraded one level for indirectness as evidence based on a single study
c. Downgraded two levels for imprecision due small sample size and low event rates

a. Downgraded one level for imprecision as sample size very small

a)

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No other outcomes were reported. **Undesirable effects for Māori** No additional evidence available	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low certainty of evidence overall **Certainty of evidence for Māori** No additional evidence available	

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment - not measured	CRITICAL	-
Adverse effects: RCT assessed with: Tolerated higher glucose infusion rates	CRITICAL	⨁◯◯◯ Very low
Adverse effects: RCT assessed with: Hypoglycaemia	CRITICAL	⨁◯◯◯ Very low
Fully breastfeeding at hospital discharge - not measured	IMPORTANT	-
Faltering growth / body composition: RCT assessed with: Weight gain (g/kg/day)	IMPORTANT	⨁◯◯◯ Very low
Faltering growth / body composition: RCT	IMPORTANT	⨁◯◯◯

assessed with: Length (measurement not specified)		Very low
Faltering growth / body composition: RCT assessed with: Head circumference (measurement not specified)	IMPORTANT	⨁◯◯◯ Very low
Duration of initial hospital stay - not measured	IMPORTANT	-
Time to full enteral feeds	IMPORTANT	⨁◯◯◯ Very low
Bronchopulmonary dysplasia (BPD) / chronic lung disease	IMPORTANT	⨁◯◯◯ Very low
Necrotising enterocolitis (NEC) - not measured	IMPORTANT	-
Sepsis: proven or suspected: RCT	IMPORTANT	⨁◯◯◯ Very low
Retinopathy of prematurity (ROP) - not measured	IMPORTANT	-
Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Fully breastmilk feeding at hospital discharge - not measured	NOT IMPORTANT	-
Time to full sucking feeds - not measured	NOT IMPORTANT	-

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	Possibly important uncertainty or variability	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability		

○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	**Insulin versus glucose reduction - very low certainty evidence** Uncertain effect on mortality, length, head circumference, bronchopulmonary dysplasia Probable decrease in adverse effects (tolerance, hypoglycaemia), sepsis Probable increase in weight Probable earlier time to reach full enteral feeds **Balance of effects for Māori** No additional evidence	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings	3 mL vial of Actrapid insulin costs approximately $8.50. Costs and savings are minimal.	

○ Varies ○ Don't know		

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Costs are moderately certain. **Certainty of evidence of required costs for Māori** No additional evidence available.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	There are no studies that assess the specific cost-effectiveness of insulin versus glucose reduction, particularly in the context of preterm infants. **Cost effectiveness for Māori** No additional evidence available.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact	**Equity for Māori** Influenced by the effects of colonisation, pēpi Māori are more likely to be born preterm, have more sepsis and neurodisability, both of which are associated	

○ Probably increased ○ Increased ○ Varies ● Don't know	with parenteral nutrition practices, and fewer survive. Thus, implementing standardised parenteral nutrition practices in Aotearoa New Zealand will contribute to achieving equitable health outcomes for preterm pēpi Māori and their whānau. **Equity for Pacific families** Implementing standardised parenteral nutrition practices in Aotearoa New Zealand will contribute directly to reducing health disparities for all ethnicities and underrepresented groups. **Equity for other underrepresented groups** Migrant and low-income families may not receive adequate explanation of hyperglycaemia management or the reasons behind specific treatments like insulin or adjusted glucose loads. This can cause confusion or distress. Equity requires staff to provide understandable, inclusive education so all families feel informed and reassured during clinical decision-making.	

Acceptability
Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Probably acceptable **Acceptability for Māori** No additional evidence available.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both interventions are feasible. **Feasibility for Māori** No additional evidence available.	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

References

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