EtD 31. Should higher feed osmolality (>450 mOsm/kg) vs. lower feed osmolality in preterm infants to reduce feed intolerance and/or necrotising enterocolitis

POPULATION:	Preterm infants
INTERVENTION:	Higher feed osmolality (>450 mOsm/kg)
COMPARISON:	Lower feed osmolality
MAIN OUTCOMES:	**Critical for making a decision** Mortality Necrotising enterocolitis (NEC) Neurodevelopmental impairment Adverse effects (other than mortality, BPD, NEC, sepsis anaemia of prematurity or ROP) feed intolerance Fully breastmilk feeding at hospital discharge **Important but not critical** Faltering growth / body composition Duration of initial hospital stay Time to full enteral feeds Bronchopulmonary dysplasia 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** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical practice recommendation: patient perspective
BACKGROUND:	Preterm infants are particularly vulnerable to feeding intolerance and gastrointestinal complications due to the immaturity of their digestive system. Osmolality, a measure of the concentration of solutes in a solution, is an important factor in the safety and tolerance of enteral feeds. Feeds with higher osmolality (e.g. >450 mOsm/kg) have been associated with delayed gastric emptying, increased risk of feed intolerance and potential for mucosal injury, which may contribute to the development of NEC, a serious and often life-threatening condition. The American Academy of Paediatrics recommends feeds of <450 mOsm/kg H2O. This recommendation remains without clear substantiation based on relevant trials, but the recommendation has led to high feed osmolality being considered to impact adverse events, particularly gastrointestinal dysfunctions and NEC. In preterm infants, feeds with an osmolality >600 (mOsm/kg H2O) have been associated with NEC. Amniotic fluid has an osmolality of 275 mOsm/kg H2O and EBM 296 mOsm/kg H2O. Amylase from the breastmilk may induce hydrolysis of the dextrin content of both breastmilk fortifier and glucose polymers, leading to small osmotically active molecules of oligosaccharides. This, in turn, increases the osmolality of the feed, making it less

	likely to be well tolerated. There is also evidence that additives can reduce the anti-infective properties of breastmilk when added too far in advance of a feed. The addition of breastmilk fortifier (especially 1¼ strength) or single nutrient additives (glucose polymers) to EBM substantially increases the osmolality. Clinical practice often involves the addition of oral medications to expressed breastmilk or other feeds prior to administration. Some medications (e.g. iron, multivitamins, some antibiotics) are hyperosmolar by nature and can significantly increase feed osmolality when added to small volumes of milk. Small volumes of 0.5–2 mL of breastmilk have been shown not to adequately dilute some medications to safe osmolality levels. For example, multivitamin preparations can raise osmolality to >800 mOsm/kg if added to <5 mL of expressed breastmilk. Determining whether higher feed osmolality increases the risk of feeding intolerance or NEC and establishing a minimum volume of breastmilk for safe medication dilution is essential to guide clinical decisions and protect this vulnerable population.
CONFLICT OF INTERESTS:	**None**

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Evidence is based on a systematic review including a human milk-based fortifier (8 RCTs, 2 observational studies) [1]. **Adverse effects: Gastric emptying**: RCT: Four of five studies reported no difference in gastric emptying for different osmolalities. One study reported delayed gastric emptying with feed osmolarity of 539 mOsm/L compared with lower levels [Critical]. **Adverse effects: Feeding intolerance**: RCT + observational study: No differences reported for feeding intolerance [Critical]. **Desirable effects for Māori** No additional data	The osmolality of breastmilk is approximately 300 mOsm/kg, but is often increased to greater than 400 mOsm/kg by the addition of breastmilk fortifiers, nutritional supplements and medications. The American Academy of Pediatrics [2] advises that formulas for normal infants should have an osmolality no greater than approximately 450 mOsm/kg. Evidence to support this recommendation has not ever been presented. Sweden [3]: Retrospective cohort: Infants <28 weeks' gestation. **NOTE:** One of the observational studies included in the Ellis 2019 review included a study that used acidified liquid human milk fortifier. This product is not available in Aotearoa New Zealand. Several studies, including [4] have indicated that the osmolality of enteral feeds exceeds the American

		Academy of Pediatrics recommendation of 450 mOsm/kg. In some cases, osmolality was equal to or exceeded 2000 mOsm/kg. Osmolality was also increased when medications were added to expressed breastmilk with fortifier compared with expressed breastmilk.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lower feed osmolarity be used	Risk difference with higher feed osmolarity (>450 mOsm/kg)
Mortality - not measured	-	-	-	-	-
Necrotising enterocolitis: RCT and observational	460 (5 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	-	Five studies (n=460) reported the effects of dietary osmolality/osmolarity on NEC and overall morbidity. An RCT reported a significantly higher NEC incidence in infants after receiving an elemental formula (650 mOsm/L) compared with a cow milk-based formula (359 mOsm/L) (87.5% vs. 25%, respectively. p<0.02). An observational study reported a significantly higher NEC incidence in infants receiving an acidified liquid fortifier (326 mOsm/kg) compared with those receiving a powdered fortifier (385 mOsm/kg) and a non-acidified liquid fortifier (385 mOsm/kg) (13%, 0% and 0%, respectively; p=0.0056). An RCT found no significant difference in NEC incidence comparing one fortifier (441 mOsm/kg) with a new fortifier with higher protein and micronutrient content (390 mOsm/kg). An observational study found no significant difference in NEC incidence with different feed osmolalities (451 mOsm/kg, 420 mOsm/kg and 378 mOsm/kg). An RCT reported no significant difference in overall morbidity (NEC and sepsis) in infants fed either a liquid fortifier (450 mOsm/kg) or a powder fortifier (385 mOsm/kg).	
Necrotising enterocolitis: Cohort study	253 (1 non-randomised study)	⨁◯◯◯ Very low[a,,]	-	This study looked at the osmolality effects of commonly used medications which included paracetamol 24 mg/mL, Sodium chloride 4 mmol/mL and fluconazole 10 mg/mL. The maximum osmolality administered was 9,600 mOsm/kg (the osmolality of undiluted oral paracetamol). The odds ratio of developing NEC after receiving solutions with an osmolality exceeding 2,000 mOsm/kg was 0.92 (P = 0.83); >800 (OR 0.48; P = 0.71) and >450 (OR 0.31; P = 0.20). 95%CI were not provided.	
Neurodevelopmental impairment - not measured	-	-	-	-	-
Adverse effects: RCT assessed with: Gastric emptying	158 (5 RCTs)	⨁◯◯◯ Very low[a,b,c,]	-	Five studies (n=158) reported effects of feed osmolality/osmolarity on gastric emptying. In one study, a mean gastric residual of 30% was found in infants 3 hours after feeding a casein hydrolysate formula (539 mOsm/L), whereas no gastric residual after feeding an 80% casein and 20% soy formula (204 mOsm/L) and 3.7% gastric residual with a casein formula (211 mOsm/L) were found. Another study found no change in gastric emptying	

				with a feed osmolality of 310 versus 155 mOsm/kg. However, gastric emptying was accelerated by decreasing osmolality from 310 to 155 mOsm/kg while increasing feed volume from 10 mL/kg to 20 mL/kg. Another study found no significant difference in gastric residuals after feeding different feeds with an osmolarity ranging from 275 mOsm/L to 576 mOsm/L. Another study reported no significant difference in gastric emptying between feeding a soybean formula containing sucrose (279 mOsm/kg) or containing glucose (448 mOsm/kg). The fifth study reported no significant difference in gastric residuals after feedings with osmolarities ranging from 340 mOsm/L to 380 mOsm/L.	
Adverse effects: RCT and observational assessed with: Feeding intolerance	408 (4 RCTs)	⨁◯◯◯ Very low[a,c,f]	-	Definitions of feeding intolerance varied among the studies but frequently included presence of abdominal distension, vomiting and delayed/with-held feedings. None of the four studies (n= 408) found significant differences in feeding tolerance with feed osmolalities up to 451 mOsm/kg.	
Fully breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Faltering growth / body composition - not measured	-	-	-	-	-
Duration of initial hospital stay - not measured	-	-	-	-	-
Time to full enteral feeds - not measured	-	-	-	-	-
Bronchopulmonary dysplasia - not measured	-	-	-	-	-
Sepsis: proven or suspected - not measured	-	-	-	-	-
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	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-

a. Downgraded one level for unclear risk of bias
b. Downgraded one level for inconsistency as studies reported different findings
c. Downgraded one level for indirectness as not all studies included a comparison >450 mOsm/kg
d. Downgraded one level for imprecision as event rates are low
e. Downgraded two levels for imprecision as OR are provided but not the confidence intervals
f. Downgraded one level for indirectness as definitions vary for feeding intolerance

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Necrotising enterocolitis (NEC)**: RCT + observational study: One study reported higher necrotising enterocolitis (NEC) incidence with feed osmolarity of 650 mOsm/L compared with 359 mOsm/L; one found higher NEC incidence with the lowest feed osmolality (326 mOsm/kg compared with 385 mOsm/kg). The remaining three studies reported no difference for NEC between osmolarities. One cohort study reported no effect on NEC with increases in osmolarity in excess of 2,000 mOsm/kg due to the addition of medications [Critical]. **Undesirable effects for Māori** No additional data	

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.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality - not measured	CRITICAL	-
Necrotising enterocolitis: RCT and observational	CRITICAL	⨁◯◯◯ Very low
Necrotising enterocolitis: Cohort study	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment - not measured	CRITICAL	-
Adverse effects: RCT assessed with: Gastric emptying	CRITICAL	⨁◯◯◯ Very low
Adverse effects: RCT and observational assessed with: Feeding intolerance	CRITICAL	⨁◯◯◯ Very low
Fully breastmilk feeding at hospital discharge - not measured	CRITICAL	-
Faltering growth / body composition - not measured	IMPORTANT	-

Duration of initial hospital stay - not measured	IMPORTANT	-
Time to full enteral feeds - not measured	IMPORTANT	-
Bronchopulmonary dysplasia - not measured	IMPORTANT	-
Sepsis: proven or suspected - not measured	IMPORTANT	-
Retinopathy of prematurity - not measured	IMPORTANT	-
Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds - not measured	NOT IMPORTANT	-

Certainty of evidence for Māori - No additional data

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Possibly some uncertainty **Values for Māori** No additional data	

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	**Higher feed osmolality versus lower feed osmolality - very low certainty evidence** Uncertain effect on gastric emptying, feeding intolerance and NEC	

● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	**Balance of effects for Māori** No additional data	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost differences between feeds or for nutritional supplements are minimal.	

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	The costs are certain. **Certainty of evidence of required resources for Māori** No additional data	

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	There are no studies that assess the specific cost-effectiveness of higher versus lower feed osmolarity in the context of preterm infants.	

comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	**Cost effectiveness for Māori** No additional data	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Equity for Māori** Pēpi Māori are more likely to be born preterm and face higher rates of NEC and feeding complications due to systemic inequities in neonatal care. If feeds with high osmolality are used without appropriate dilution, the risk of harm may increase, particularly where resources or staff training are inconsistent. Whānau Māori may not be included in discussions about feed safety, medication administration or the role of breastmilk in reducing risk. Equity requires culturally safe care, standardised guidelines and transparent communication to ensure all pēpi Māori receive safe, well-tolerated feeds that support gut health and early development. **Equity for Pacific families** Pacific families may not be informed about how feed osmolality affects their baby's tolerance or risk of complications. If feeding plans are not clearly explained, families may feel excluded from important decisions. Equity requires culturally appropriate communication that builds understanding and trust in feeding strategies tailored to each infant. **Equity for underrepresented groups** Families from migrant or low-income backgrounds may not receive consistent explanations about the safety of higher or lower osmolality feeds. Without clear information, they may not understand changes in feeding tolerance. Equity means ensuring all families receive simple, accessible guidance to participate fully in decisions affecting their baby's nutrition.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Acceptability of the intervention may vary.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The intervention is feasible.	

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	**Possibly important**	Probably no important	No important			

	JUDGEMENT						
	or variability	**uncertainty or variability**	uncertainty or variability	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

1. Ellis, Z.M.; Tan, H.S.G.; Embleton, N.D.; Sangild, P.T.; van Elburg, R.M. Milk feed osmolality and adverse events in newborn infants and animals: a systematic review. *Arch Dis Child Fetal Neonatal Ed* **2019**, *104*, F333-f340, doi:10.1136/archdischild-2018-315946.
2. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant In *Pediatric Nutrition Handbook* 5ed.; Ilinois, 2003; Vol. 5, p. 23.
3. Latheef, F.; Wahlgren, H.; Lilja, H.E.; Diderholm, B.; Paulsson, M. The risk of necrotizing enterocolitis following the administration of hyperosmolar enteral medications to extremely preterm infants. *Neonatology* **2021**, *118*, 73-79, doi:10.1159/000513169.
4. Chandran, S.; Chua, M.C.; Lin, W.; Min Wong, J.; Saffari, S.E.; Rajadurai, V.S. Medications that increase osmolality and compromise the safety of enteral feeding in preterm infants. *Neonatology* **2017**, *111*, 309-316, doi:10.1159/000454667.

Back to question list