EtD 9. Should fish oil only based lipids (Omegaven) vs. Multi-component lipids (SMOFlipid) be used for prevention or rescue therapy for preterm infants with (any cause) liver disease?

POPULATION:	Preterm infants in neonatal care
INTERVENTION:	Fish oil only based lipids (Omegaven)
COMPARISON:	Multi-component lipids (SMOFLipid)
MAIN OUTCOMES:	**Critical outcomes** Mortality Adverse effects (prevention of PN associated liver disease) Faltering growth/body composition Retinopathy of prematurity Bronchopulmonary dysplasia **Important but not critical** Neurodevelopmental impairment Fully breastfed or breastmilk feeding at hospital discharge Time to full enteral feeds Duration of initial hospital stay Sepsis: proven or suspected Necrotizing enterocolitis Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Less important for decision making** Time to full sucking feeds Resolution of PNALD/cholestasis; Growth rate; Death before discharge; Incidence PNALD/cholestasis; Head growth velocity; Any sepsis;
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	Liver disease in preterm infants, including intestinal failure-associated liver disease is a significant complication of prolonged parenteral nutrition (PN). Lipid emulsions are a key component of PN, providing essential fatty acids and energy, but their composition can influence liver health. Most Aotearoa New Zealand neonatal units use multicomponent lipid emulsions. These containing a mix of soybean, coconut, olive, and fish oils, and aim to balance essential fatty acid provision with reduced pro-inflammatory components, offering a broader spectrum of nutrients. While they may not achieve the same anti-inflammatory effect as fish oil only lipids (FOLE), multicomponent emulsions can provide more comprehensive nutritional support and are less expensive than fish oil only emulsions. Fish oil-based lipid emulsions, rich in omega-3 fatty acids, have been proposed as both a preventive and rescue therapy for liver conditions. These emulsions have anti-inflammatory and immunomodulatory properties, reduce oxidative stress, and may promote bile flow, which can mitigate cholestasis and liver injury. However, fish oil only lipids provide lower amounts of energy and omega-6 fatty acids, potentially

	limiting their capacity to fully support growth and development when used as the sole lipid source.
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 from a Cochrane review [1] another systematic review [2] and a retrospective review of cases [3]. The Cochrane review [1] included a subgroup analysis of preterm infants with surgical conditions or cholestasis. The review found no evidence from randomised studies to determine with any certainty if fish oil only lipid emulsions offer an advantage in the prevention or resolution of cholestasis or in any other clinical outcome compared with multicomponent lipid emulsions in infants with liver disease. The Park review reported: **Adverse effects (Recovery of intestinal failure associated cholestasis):** Pooled data - RCT and cohort studies: Use of fish oil was associated with an extremely large and significant increase in recovery from intestinal failure associated cholestasis (403 more per 1,000; 160 more to 606 more). [Critical] **Desirable effects for Māori** No additional evidence available	Cochrane review [1] included preterm infants <37 weeks' gestation and included infants with surgical conditions or intestinal failure-associated liver disease/cholestasis. Systematic review by Park *et al* [2] included neonates with parenteral nutrition associated cholestasis. Majority were between 23 and 36 weeks. The Ramiro-Cortijo [3] retrospective review of medical charts of neonates who were changed to Omegaven after the diagnosis of cholestasis while receiving SMOFlipid (i.e. a multicomponent lipid emulsion was replaced by a fish oil only lipid emulsion. Thirty-eight infants (92.1% preterm, being 44.7% born below 28 weeks' gestation), received fish oil only lipid emulsion. 1 g/kg/day. **NB The usual lipid dose is 3 g/kg/day,** so in addition to the change of lipid emulsion, they also had a **33% reduction in lipid emulsion**, which also improves liver function. Additional experiential evidence was identified in a USA single-arm observational study using fish oil-based lipid emulsions for the treatment of intestinal failure-associated liver disease [4]. The median gestational age at birth of the 97 infants was 28 weeks (range 22.7–40 weeks). Eighty-three (86%) survived with resolution of cholestasis and 14 (14%) died.

		The median conjugated bilirubin concentration at the initiation of therapy was 4.8 mg/100mL (range 2.1–26). The median time to resolution of cholestasis was 40 days (range 3–158).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with multi-component lipids (SMOFLipid)	Risk difference with HQE 1.6.b fish oil only based lipids (FOLE) (Omegaven)
Mortality - not reported	-	-	-	-	-
Adverse effects (prevention of PN associated liver disease): 1 RCT, 1 controlled trial, 2 cohort studies	1101 (4 non-randomised studies)	⨁⨁◯◯ Low	**OR 0.56** (0.28 to 1.10)	Study population	
				51 per 1,000	**22 fewer per 1,000** (36 fewer to 5 more)
Adverse effects (prevention of PN associated liver disease): retrospective chart review	0 (1 non-randomised study)	⨁◯◯◯ Very low[a,b,c]	-	In 73.7% (28/38) of the neonates, the cholestasis was resolved. In 34.2% (13/38), resolution happened before FOLE discontinuation. In addition, in the rest of the neonates (15) in whom cholestasis resolved, resolution occurred after FOLE discontinuation.	
Adverse effects (recovery from PN associated liver disease): 1 RCT, 2 cohort studies	93 (3 non-randomised studies)	⨁⨁◯◯ Low[d]	**OR 6.14** (2.27 to 16.60)	Study population	
				196 per 1,000	**403 more per 1,000** (160 more to 606 more)
Faltering growth/body composition - not measured	-	-	-	-	-
Retinopathy of prematurity - not measured	-	-	-	-	-
Bronchopulmonary dysplasia - not measured	-	-	-	-	-
Neurodevelopmental impairment - not measured	-	-	-	-	-
Fully breastfed or breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Time to full enteral feeds - not measured	-	-	-	-	-
New outcome - not measured	-	-	-	-	-
Sepsis: proven or suspected: retrospective chart review	38 (1 non-randomised study)	⨁◯◯◯ Very low[a,b,c]	-	No differences were found in sepsis incidence before and after initiation of FOLE ($\chi 2 = 3.014$; p-Value = 0.32).	
Necrotizing enterocolitis - 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 two levels for risk of bias as this is a retrospective chart review
b. Downgraded two levels for indirectness as evidence is based on a single study with no direct comparison
c. Downgraded three levels for risk of bias as this a retrospective chart review with no direct comparison
d. Downgraded two levels for imprecision due to extremely large confidence intervals

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Kapoor 2019 [1]: The review included a subgroup analysis of preterm infants with surgical conditions or cholestasis. There is currently no evidence from randomised studies to determine with any certainty if fish oil only lipid emulsions offer a disadvantage in the prevention or resolution of cholestasis or in any other clinical outcome compared with multicomponent lipid emulsions in infants with liver disease. **Adverse effects (prevention of intestinal failure-associated liver disease):** RCT and cohort studies: No significant reduction in prevention of **intestinal failure-associated liver disease** (22 fewer per 1,000; 36 fewer to 5 more). [Critical] **Adverse effects (prevention of intestinal failure-associated liver disease):** Retrospective chart review: In 73.7% (28/38) of the neonates, the cholestasis was resolved. In 34.2% (13/38), resolution happened before fish oil only lipid emulsions discontinuation. In addition, in the rest of the neonates (15) in whom cholestasis resolved, resolution occurred after fish oil only lipid emulsion discontinuation. [Critical] **Sepsis:** Retrospective chart review: No differences were found in sepsis incidence before and after initiation of fish oil only lipid emulsion ($\chi 2 = 3.014$; *p*-Value = 0.32). **Undesirable effects for Māori** No 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	Low to very low certainty of evidence overall. **Certainty of evidence for Māori** No additional evidence available	

Outcomes	Importance	Certainty of the evidence (GRADE)
Adverse effects (prevention of PN associated liver disease): 1 RCT, 1 controlled trial, 2 cohort studies	CRITICAL	⨁⨁◯◯ Low
Adverse effects (prevention of PN associated liver disease): retrospective chart review	CRITICAL	⨁◯◯◯ Very low
Adverse effects (recovery from PN associated liver disease): 1 RCT, 2 cohort studies	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition - not measured	CRITICAL	-
Retinopathy of prematurity - not measured	CRITICAL	-
Bronchopulmonary dysplasia - not measured	CRITICAL	-
Neurodevelopmental impairment - not measured	IMPORTANT	-
Fully breastfed or breastmilk feeding at hospital discharge - not measured	IMPORTANT	-
Time to full enteral feeds - not measured	IMPORTANT	-
New outcome - not measured	IMPORTANT	-
Sepsis: proven or suspected: retrospective chart review	IMPORTANT	⨁◯◯◯ Very low
Necrotizing enterocolitis - 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	-

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 important uncertainty or variability. **Values for Māori** No additional evidence available	

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	**Rescue therapy: Effect of fish oil only based lipids compared with multi-component lipid emulsions - Low certainty evidence** Increase in recovery from intestinal failure-associated liver disease **Prevention: Effect of fish oil only based lipids compared with multi-component lipid emulsions - Very low certainty evidence** Uncertain effect for adverse effects (prevention of intestinal failure associated liver disease), sepsis **Balance of effects for Māori** No additional evidence available	There is no evidence that fish oil only based lipids compared with multi-component lipid emulsions prevent intestinal failure in preterm infants. **Vote was on** the effect of fish oil only based lipids compared with multi-component lipid emulsions **as rescue therapy for intestinal failure**

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Costs for lipid emulsions:** SMOFLipid including vitamins per syringe approx. $51 to $71 (used for 48 hours) = $25.50 to $35.50 per day Omegaven, including vitamins per syringe approx. $110 (used for 24 hours) = $110 per day **Cost difference $74.50 to $84.50 per day** **$745 to $845 per 10 days**	

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 Aotearoa New Zealand costs are reasonably certain. **Resourcing 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	No economic studies were identified to address the cost-effectiveness of the intervention or the comparison. **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 ● Probably increased ○ Increased ○ Varies ○ Don't know	**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 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 underrepresented groups** Access to fish oil-based lipid therapy may depend on regional availability or clinician experience, which can disadvantage infants in smaller centres. Families unfamiliar with such treatments may require additional support. Equity means ensuring therapies are available across all hospitals and explained in ways that are accessible to every family.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is likely to be acceptable to stakeholders but would cost more. **Acceptability for Māori** There is no evidence to suggest the intervention would not be acceptable.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Fish oil only lipid emulsion is in widespread use as rescue therapy for preterm infants in Aotearoa New Zealand, so it is feasible here. **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**

	JUDGEMENT						
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. Kapoor, V.; Malviya, M.N.; Soll, R. Lipid emulsions for parenterally fed preterm infants. *Cochrane Database Syst. Rev.* **2019**, *6*, CD013163, doi:10.1002/14651858.CD013163.pub2.
2. Park, H.W.; Lee, N.M.; Kim, J.H.; Kim, K.S.; Kim, S.N. Parenteral fish oil-containing lipid emulsions may reverse parenteral nutrition-associated cholestasis in neonates: a systematic review and meta-analysis. *J. Nutr.* **2015**, *145*, 277-283, doi:10.3945/jn.114.204974.
3. Ramiro-Cortijo, D.; Del Pozo Arribas, S.; Inisterra Viu, L.; Vazquez, N.G.; Saenz de Pipaon, M. Exclusive fish oil lipid emulsion rescue strategy improves cholestasis in neonates on partially fish oil-based lipid emulsion: A pilot study. *Nutrients* **2023**, *15*, doi:10.3390/nu15030509.
4. Premkumar, M.H.; Carter, B.A.; Hawthorne, K.M.; King, K.; Abrams, S.A. Fish oil-based lipid emulsions in the treatment of parenteral nutrition-associated liver disease: an ongoing positive experience. *Adv. Nutr.* **2014**, *5*, 65-70, doi:10.3945/an.113.004671.

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