

FEEDING FOR PRETERMS (FP) SYNTHESIS

Research Gaps from Cochrane Reviews (Cochrane Library Issue 3, 2006)

The faces indicate the direction of findings in each review:

- ☺ **Likely to be effective**
- ☹ **Both benefits and risks**
- ❓ **Uncertain or limited effect**
- ☹ **Likely to be ineffective or potentially harmful**

Important research implications are more likely to arise from reviews with uncertain findings or where the benefits and risks are mixed

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TIMING OF FEEDING

- ☹ **Not clear if ad-libitum, demand, semi-demand or scheduled feeds are more effective (Tosh 2006)**
Need a large RCT of ad libitum or demand/semi-demand feeding versus scheduled interval feeding; focusing first on those preterm infants at the transition from enteral tube to oral feeding. Involvement of parents would inform the selection of the most relevant outcomes including those related to parental satisfaction.
- ☹ **Not enough data to determine the optimum time for commencement of enteral feeds in pre-term infants being fed parenterally (Kennedy 2000)**
Needs to be determined as there are risks and benefits associated with both early (less than 4 days) and late commencement. This will require a large RCT in which the clinicians do not have strong preferences for age at which enteral feeding should start. Trial outcomes should include: death before discharge, death or NEC requiring surgical resection before discharge, death or very prolonged hospital stay, death or major morbidity (including severe developmental delay and short bowel syndrome) at follow-up.
- ☹ **Using a formal feeding readiness assessment instrument compared to no formal instrument in preterm infants deemed ready to commence feeds (Crowe 2006)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
- ☹ **The effect of different rates of advancement of enteral feeding beginning at the same postnatal age in premature infants as measured by feeding tolerance and neonatal outcome (Kennedy 1998)**

Need a large trial comparing different rates of advancement of feeding among infants less than 1000g birth weight which assesses death before discharge; death or NEC requiring surgical resection before discharge home; death or very prolonged hospital stay (outcome associated with major long-term morbidity and addressing NEC, sepsis, other major long-term major complications of prolonged parenteral nutrition); death or major morbidity at follow-up

BREASTFEEDING

- ☹ **Not clear if there is any advantage in avoiding bottle feeds in preterm infants (Collins 2005)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
 - ☹ **Not clear if cup feeding is better in achieving breastfeeding than other forms of supplemental enteral feeding in (preterm) infants unable to fully breastfeed (Flint 2005)**
 - Cochrane protocol
 - Cochrane review in progress
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METHODS OF FEEDING

- ☹ **Not clear if intermittent nasogastric tube milk feeding is more effective than continuous feeding (Premji 2002)**

Future trials need to rigorously define feeding protocols and feeding intolerances and stratification should be attempted for birthweight, gestation and severity of illness.
- ☹ **Not clear if home (early discharge) gavage is more effective than hospital gavage although one trial of home gavage shows some promise (Collins 2003)**

Need for trials with concealed random allocation, complete follow-up and adequate sample size to evaluate infection rates, feeding and growth, health care costs, impact of family, complications of gavage feeding and long term developmental outcomes of preterm infants allocated to early discharge with home gavage feeding compared with traditional hospital care
- ☹ **Short-term benefits of early lipid administration for parenterally fed infants not seen (Simmer 2005)**

Need RCT with sample size adequate to estimate effects on long-term growth, respiratory and neurodevelopmental outcomes, concentrating on infants less than 28 weeks gestation as these infants have high risk of short term morbidity, mortality and long term neurodevelopmental sequelae.
- ☹ **Early i.v. nutrition versus routine i.v. fluids for preterm infants who are not being fed enterally to prevent jaundice (Faber 2003)**

No trials of early i.v. nutrition versus routine i.v. fluids for preterm infants who are not being fed enterally, which report outcomes for neonatal jaundice
- ☹ **No studies of feed thickeners for gastro-oesophageal reflux in preterm (or term) infants (Huang 2002)**

Need RCT of sample size at least 50 infants, outcomes should include GOR (regurgitation, possetting, vomiting, haematemesis, failure to thrive, irritability, disturbed sleep, cough, apnoeas, oxygen desaturation, bradycardias), gastric and oesophageal acidity based on pH monitoring and side effects of the therapy (bowel obstruction, diarrhoea, aspiration, cough and colic)
- ☹ **Non-nutritive sucking has some benefits such as reduced hospital stay (Pinelli 2005)**

Studies addressing long-term outcomes and using similar outcomes to existing studies are needed
- ☹ **Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates (Ainsworth 2004)**

One study suggests that the use of percutaneous central venous catheters rather than peripheral cannulae is associated with significantly smaller deficit in delivered parenteral nutrition with no difference seen

for rate of infection in 3 studies but there were no data on longer term growth and developmental outcomes, which is particularly important for very preterm infants

- ☺ **Push feeding versus gravity feeding for more rapid establishment of full gavage tube feeds in preterm and/or low birth weight infants who require intermittent bolus tube feeding (Dawson 2005)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
 - ☺ **Effects of commencing TPN at higher amounts of amino acid (Thomas 2006)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
 - ☺ **Transpyloric versus gastric tube feeding for preterm infants (McGuire 2002)**

Not a priority for further research due to lack of evidence of benefit combined with finding of an increased risk of gastrointestinal disturbance
 - ☺ **Trophic feeding for parenterally fed infants (Tyson 2005)**
 - Large multi-centre trial of trophic feedings is needed among infants 1000g birthweight or less
 - Requires a trial sufficiently large to identify important effects on the following variables:
 - death before discharge home;
 - death or NEC requiring surgical resection before discharge;
 - death or very prolonged hospital stay (outcome associated with major long-term morbidity including NEC, sepsis and other major complications of parenteral nutrition);
 - death or major morbidity (including severe developmental delay and short bowel syndrome) at 18 months adjusted age
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HUMAN MILK COMPOSITION

- ☺ **Calcium and phosphorus supplementation of human milk for preterm infants (Kuschel 2001)**

No trials of calcium and phosphorus supplementation alone
- ☺ **Carbohydrate supplementation of human milk for preterm infants (Kuschel 1999)**

No trials of carbohydrate supplementation
- ☺ **Fat supplementation of human milk for preterm infants (Kuschel 2000a)**

Any future trials of fat supplementation should focus on short term, long term and adverse outcomes (feed intolerance, NEC, diarrhoea) associated with medium-chain triglyceride supplementation and should contain adequate sample sizes in order to demonstrate any effect
- ☺ **Protein supplementation of human milk for preterm infants (Kuschel 2000b)**

Some benefits from of protein supplementation but the long-term benefits have not been explored and further trials including large sample sizes are required
- ☺ **High versus low medium chain triglyceride content of formula for promoting short term growth of preterm infants (Klenoff-Brumberg 2002)**

No evidence from 5 RCTs of a difference between high and low MCT formula on short term growth, gastrointestinal intolerance or the incidence of NEC although this may not have been sufficiently powered to show any effect. Further studies are needed with larger sample sizes and careful blinding of outcome assessors (to assess gastrointestinal intolerance) in order to adequately answer effect of high versus low MCT formula on short and long term growth parameters and long term neurodevelopmental outcomes
- ☺ **Multicomponent fortified human milk for promoting growth in preterm infants (Kuschel 2004)**

Future research should be aimed at determining the ‘optimal’ composition of multicomponent fortifiers

- ☺ **Multicomponent fortified human breast milk versus unfortified breast milk in preterm or low birth weight infants following hospital discharge (McGuire 2004b)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
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FORMULA MILK COMPOSITION

- ☺ **Calorie and protein-enriched formula milk versus standard formula (Henderson 2005)**

Need larger trials that assess long term outcomes such as final height, body composition and neurodevelopment (and participants in existing trials need to be followed up long term)
 - ☺ **High protein formula (Premji 2006)**
 - Some benefits (such as weight gain) but short- and long-term growth and neurodevelopmental morbidities associated with increasing protein intake are still unclear - protein intakes above 4g/kg/day should be considered experimental
 - Future research should also aim to determine the precise protein requirements of preterm infants according to birth weight and gestational age
 - ☺ **Longchain polyunsaturated fatty acid supplementation in preterm infants (Simmer 2004)**
 - Benefits or risks have not been identified.
 - Any future studies should be in very preterm infants who may benefit more – see Commentary below
 - ☺ **Preterm compared with term formula among low birth weight or preterm infants (Bell 2003)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
 - ☺ **Soy formula in preterm infants (Osborn 2006)**

This review has been withdrawn as of Cochrane Library Issue 2, 2006
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FORMULA VERSUS HUMAN MILK

- ☺ **Formula milk versus term preterm human milk for feeding term or low birth weight infants (Henderson 2001a)**
 - Need to compare nutrient fortified preterm breast milk with formula milk
 - Could compare donated preterm breast milk versus formula milk
 - ☺ **Formula milk versus term human milk for feeding preterm or low birth weight infants (Henderson 2001b)**
 - Old studies show improved short term growth for formula compared with unfortified human term milk - further studies are needed comparing enteral feeding with nutrient-enriched ‘pre-term’ formula milk versus nutrient-fortified term human milk in a population at increased risk of NEC (e.g. very low birth weight infants (<1500grams))
 - When no breast milk is available, could the supplementation of formula milk with a breast milk factor, such as immunoglobulin, reduce the incidence of NEC?
 - Future trials should attempt to ensure that carers and assessors are blinded
 - Future trials regarding risk of NEC would require a sample size of approximately 900 infants
 - ☺ **Not clear if calorie and protein-enriched formula milk is more effective than human breast milk in preterm or low birth weight infants following hospital discharge (McGuire 2004a)**
 - Cochrane protocol
 - Not yet covered in a Cochrane review
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FORMULA OR HUMAN MILK

☺ **Increased energy intake compared with standard energy intake in preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease (Lai 2006)**

- No RCTs were located, so need to assess the optimal levels of energy intake, the best methods of delivering such levels of intake, and the optimal combination of various constituents of energy in preterm infants at risk of lung disease, as well as possible adverse effects from various methods of increasing energy intake. Target population should include all preterm infants with established or developing CLD/BPD. Outcomes should include short and long term respiratory morbidities and mortality, growth and neurodevelopment. Complications that might be related to CLD/BPD, like death from respiratory causes, should be assessed as an outcome and not constitute grounds for exclusion.

☺ **Lactase treated feeds to promote growth and feeding tolerance in preterm infants (Tan-Dy 2005)**

- Need RCTs of lactase-treated feeds enrolling very preterm infants when enteral feeds are commenced measuring primary outcomes such as weight gain (g/kg/day); growth expressed as weight, length and head circumference percentile for gestational age, assessed at birth and at 40 weeks post-menstrual age; and days to achieve full enteral feeds and secondary outcomes such as duration of parenteral nutrition; days enteral feeds held; number of times enteral feeding is interrupted for gastric residuals; duration of hospitalization; incidence of NEC; incidence of bacteraemia and sepsis; incidence of CLD; and other adverse effects
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DRUG INTERVENTIONS

☺ **Erythromycin for feeding intolerance in preterm infants (Ng 2001)**

No studies including only infants with feeding intolerance were located - need large RCTs including only infants with feeding intolerance and using lower than antimicrobial doses – see Commentary below

COMMENTARY

Timing of feeding

- Trials of when to commence enteral feeds, how to determine feeding readiness and rate of advancement of enteral feeding are seen as important trials that need to be undertaken.

Breastfeeding

- Important to establish the effects of avoiding bottle feeds in preterm infants
- Need to establish if benefits of cup feeding are outweighed by nursing resources required

Methods of feeding

- Important to know whether home gavage is more effective than hospital gavage
- Important to do trials assessing early i.v. nutrition for preventing jaundice
- Important to establish whether feed thickeners are effective
- A trial of central catheters versus peripheral cannulae for delivering parenteral nutrition is needed
- Further studies of non-nutritive sucking are not a high priority since there is evidence in support of non-nutritive sucking
- Trials of trophic feeding are not a high priority since early trophic feeding is generally accepted
- Trials involving transpyloric feeds are not encouraged because of the risks associated with this form of feeding

Human milk composition

- Trials of calcium and phosphorus supplementation alone are needed
- Further trials of energy (carbohydrate/fat) supplementation are needed
- Awaiting the results of the DINO trial (ACTRN012606000327583) for further knowledge about the effects of longchain polyunsaturated fatty acid supplementation in preterm infants

Formula versus human milk

- Trials comparing formula and human milk are of moderate priority

Drug interventions

- Several more trials have now looked at erythromycin for feeding intolerance in preterm infants – showing mixed results – so the Cochrane review requires updating

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