



NEOMUNE research platform – work package synopses

WP 1.4a: Donor human milk to preterm infants

<p>1. Related WPs, MG contact person: Synergies with WP 1.4b, 1.6a, 1.7, 2.3, 2.4. MG contact: Per Sangild</p>
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<p>3. Main aim and sub-aims Aim: To determine whether (supplemental) human donor milk has beneficial effects (in terms of reduction of infectious episodes and mortality) when compared to (supplemental) preterm formula during the first 10 days of life in very low birth weight (VLBW) infants. Sub-aims: To determine if early use of donor milk results in a more diverse intestinal colonization, earlier attainment of full enteral feeding, reduced number of days on parenteral nutrition, similar growth rate, similar bone density and improved Bayley Scores of Infant Development III at 2 years, compared with infants fed preterm formula.</p>
<p>4. Background and a central hypothesis: Feeding own mother's milk (OMM) to preterm neonates is thought to have important beneficial effects for VLBW infants when compared to formula feeding. Short-term effects seem to include a reduction in the incidence of sepsis and necrotizing enterocolitis (NEC). Neonatal sepsis, occurring in 20-60% of VLBW infants, is a major contributor to neonatal morbidity and mortality and compromised long term neurodevelopmental outcome. Unfortunately, it has proven to be very difficult to provide OMM within the first few hours and days of life as the onset of lactation is often delayed after preterm delivery. <i>We hypothesize that a diet completely consisting of human milk (OMM and/or donor milk) during the first 10 days of life reduces the incidence of sepsis/NEC and/or mortality in VLBW infants.</i></p>
<p>5. Key analyses and methods: Blinded randomized controlled multicenter study, conducted in 5 Dutch hospitals. Infants with a birth weight <1500 grams will be included after obtaining informed consent. The intervention starts when the first enteral nutrition (MEF) is given according to the local protocol. If milk of the own mother is available this will always be used first in both groups. If milk of the own mother is not available, or the volume is not sufficient, infants in group A will receive donor milk and infants in group B will receive infant formula. The study intervention ends at day 10 of life and OMM or donor milk will not be fortified during these days, to avoid introduction of cow's milk protein before day 10 of life. Data on the primary and secondary endpoints will be collected until 60 d of age. We consider a reduction in the combined incidence of serious infections and/or NEC and/or death from 40% in the control group to 25% in the donor milk group to be clinically relevant.</p>
<p>6. Expected results: Data will be collected on the incidence of the combined outcome of serious late-onset infections (sepsis/meningitis and NEC) and/or death occurring between age 72 hours and 60 days. Additionally, the</p>



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composition of fecal microbiota (first stool and stool at days 10 and 30), time to full enteral feeding, days on parenteral nutrition, weekly growth rate (body weight, length and head circumference), bone density by ultrasound and Bayley Scores of Infant Development III at 2 years of age will be determined. We will determine differences in these outcomes between VLBW infants fed with a diet completely consisting of human milk and VLBW infants (partly) fed with formula during the first 10 days of life.

7. Estimated time frame

Task	2011				2012				2013				2014				2015				2016			
Planning, protocol	x	x	x	x																				
Sample collection					x	x	x	x	x	x	x	x	x	x	x	x								
Data analyses															x	x								
Analyses feces									x	x	x	x	x	x	x	x								
Publication(s)																	x	x						

8. Estimated budget from NEOMUNE: 1.0 mio DKK

Also used to support participation and consulting in WPs 1.4b, WP 1.6a and WP 1.6b.

9. Estimated budget from elsewhere: 0.8 mio €

Mead Johnson Nutritional.

10. Additional comments:

- There is important scientific synergy to a number of other NEOMUNE projects on feeding preterm infants or preterm pigs (see section 1). As such, there is a possibility to make use of shared analytical capacity and/or knowledge sharing in the areas of gut microbiota, immunity, metabolism and brain-related endpoints. Possible analyses of samples within the NEOMUNE network will be determined after completion of the intervention studies.
- The Amsterdam group has intensive experience on nutrition research in preterm infants and in using pigs as models for infants. The leader of the Amsterdam group is a central opinion leader for nutrition in preterm infants via ESPGHAN. Central role in leading WP 1.4b.
- The Amsterdam group is important in planning the NEOMUNE intervention studies on preterm infants in China and is already leading infant nutrition studies in China.
- The Amsterdam group may be important as a training site for researchers from elsewhere in NEOMUNE, including WP 1.7.



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WP 1.4b: Database of feeding preterm infants

1. Related WPs, MG contact person: Synergies with WP 1.4-6, MG contacts: Per Sangild, Gorm Greisen

2. Key involved personnel, institution and mail address (project leader + main study site underlined):

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3. Main aim and sub-aims:

Aim: To provide insight in nutritional practices and use of anti-/probiotics in preterm infants < 1500 grams in various hospitals and multiple countries around the world. This baseline information will then constitute the basis for intervention studies in the near future.

Sub-aims: 1) to determine possible associations between nutritional practices and clinical outcomes. 2) to relate different practices to biological and cultural factors (in connection with WP 1.7); 3) To calculate actual energy and protein intake and to compared this with (local) recommendations; 4) To determine changes in feeding practices over time.

4. Background and central hypotheses:

Poor nutrition and impaired growth of premature infants is associated with adverse consequences in the long term. Over the last decades knowledge on nutrition of preterm infants has accumulated and clinical guidelines on nutritional requirements have been regularly revised. Nevertheless, the exact nutritional needs of VLBW infants remain uncertain. In addition, extra-uterine growth restriction is still the rule rather than the exception in VLBW infants and is associated with impaired neurocognitive development later in life.

We hypothesize that 1) the time to achieve full enteral feeding (TFF, in this study set at 120 mL/kg/d) differs widely among hospitals, and variation in TFF is associated with type of diet and antibiotics use; 2) infants in units that achieve enteral feeding 120mL/kg/day earlier achieve higher body weight at the end of follow-up when corrected for GA and weight at birth; 3) differences in feeding practice is not significantly associated with differences in major neonatal morbidities.

5. Key analyses and methods:



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Collection of retrospective and prospective data from 17 hospitals worldwide into a web-based database. The participating hospitals will enter the data of eligible infants from 1 January 2011 to 15 September 2013, retrospectively, and from 16 September 2013 to 15 September 2014, prospectively. Formation of the web-based database is led by Marita de Waard and Hans van Goudoever. Marita and Yanqi Li will lead the communication with hospitals, collection of data, and data analyses.

6. Expected results:

The database collects data from preterm infants <1500 g from the first day of birth to 37 weeks gestational age or discharge, whichever comes first, in the 17 participating hospitals. The data include timing and composition of parenteral and enteral nutrition, growth, timing and determination of administered antibiotics and probiotics, protein and energy intake, incidence of NEC stage II or III, duration of admission in hospital and maternal data.

Each parameter will be compared among hospitals to investigate whether they differ and correlations among parameters will be done to identify relationships between nutritional and –biotics practices and clinical outcomes. The observational data will provide indirect evidence for the optimal feeding regimen and will constitute a basis for identifying the most important variables that affect clinical practices in different parts of the world.

7. Estimated time frame

Task	2013			2014			2015			2016			2017		
Planning, database development	x	x	x												
Data entry			x	x	x	x									
Data analyses in each hospital						x	x	x							
Overall collective data analyses							x	x	x	x					
Publication(s), individual hospital*							x	x	x						
Collective overall publication(s)*									x	x	x				

* Data are allowed to be analyzed in individual hospitals for their internal use or publishing on local or international journals. To retain the novelty of the overall collective data, comparison of data among different hospitals is not allowed until after the publication of the overall collective data.

8. Estimated budget from NEOMUNE: 0.4 mio DKK

9. Estimated budget from elsewhere: PhD/post doc salaries (3 yrs, 30%, Marita, Yanqi): 0.9 mio DKK
Support from local hospital sites (man power to collect data, 16 x 5% salary): 0.5 mio DKK

10. Additional comments:

- The personnel who perform the data entry are provided by each participating hospitals.
- The data base work is also instrumental in letting people come together and discuss the rationale for the clinical procedures taking place at different hospitals and in different countries.
- Regarding the authorship for future collective publications, we propose that we include everyone who contributes to the database work as the author. On the publication, the names of 1-3 junior authors (who contribute the most) are shown and the rest is shown as the Database group. An author list allowing 50 names with an alphabetical ordering is used to specify the Database group, and in this way every author can be indexed in pubmed.
- Base on this database work, we are discussing with SYSU about further collaborations to 1) follow-up the growth and brain development of infants recruited in this database from selected hospitals (e.g. FWCH) for up to two years; 2) investigate whether different feeding practices for preterm infants among different hospitals in east and west are related to cultural factors. These two side-projects are at very preliminary stage and depend on whether we can get extra budget. Zhu Yanna and her colleagues at SYSU aim for applying Chinese funds in 2014 in collaboration with NEOMUNE.