Breakout Session #3: Neonatal Gastrointestinal Injury

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International Neonatal Consortium

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By WebEx

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Response to Breakout Question #1 (1)

- For neonatal gastrointestinal injury, what indication(s) are in most need of effective therapies (e.g. prevention of necrotizing enterocolitis (NEC), treatment of NEC)? Include an estimate of the incidence and severity.

1. Prevention of NEC
2. Treatment of NEC

- As more babies survive the first week so NEC has become proportionately more important as a cause of mortality and morbidity
- Determining the incidence is complicated by lack of a robust case definition

- Incidence increases at lower gestational age, variable but 'proven' cases around 7-15% ≤28 weeks, mortality 20 to 30%, neurodevelopmental delay in around 25% survivors with nutritional problems related to short gut in surgical survivors.
- Rare but devastating; international collaboration essential to crack problems

Response to Breakout Question #1 (2)

some comments that don't fit in elsewhere

- Breast milk affords some protection
- We remain ignorant about optimal time of introduction and rates of progression of enteral feeds
- Trials of any new drugs should be undertaken against a background of optimal use of breast milk
- Interventions currently of interest include live 'probiotic' bacteria and milk derived products such as lactoferrin
- Advice to clinicians about the regulatory status of these products is sometimes inconsistent

Response to Breakout Question #2

- For prevention or treatment of NEC, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?
  - **What juvenile animal toxicity studies are needed?** Consider single- and repeat-dose studies in relevant juvenile animal models for both pharmacological effect and toxicity profile
  - **Are animal models available for the indication** (e.g. gestational age equivalent)? Yes, disease assessments in the neonatal rodent and porcine models have been used to test pharmacological activity in necrotizing enterocolitis.
  - **Can the non-clinical data be extrapolated to inform clinical development, including initial dosing?** It is not clear that these models have been successfully extrapolated to the clinical setting.

Response to Breakout Question #2

- For prevention or treatment of NEC, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?

- With the increasing availability of in-vivo and high throughput methodologies why are animal models still needed?

- Animal models still useful for undertaking mechanistic studies, studies of safety and identifying candidate medicines

- Important to understand different rodent & porcine models in terms of insult and developmental status of animal. Need to be very cautious extrapolating findings to infants.

Response to Breakout Question #3

- For prevention or treatment of NEC, what information would be needed before starting a clinical trial?
  - **Can existing pediatric or adult studies be extrapolated to neonates?** No, but it was questioned whether we should re-visit the potential of cisapride to increase intestinal mobility
  - **Could a master protocol be developed for use when evaluating treatments for this indication?** Yes, but different master protocols needed for preventative and treatment drugs and modification might be needed because of safety profile and the method of administration of the intervention – some clinicians might be resistant to giving early oral medication to a high risk infant. …….
  - Entry criteria and enteral feeding regimen should be standardised as far as possible. …… (???antibiotic usage)
  - Outcomes: agreed robust case definition urgently needed
  - Cluster design perhaps needed for interventions that modify microbiome.

Response to Breakout Question #4

- Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies)? Is there equipoise?

- A major impediment is the need for an internationally agreed case definition
- Also the need for improved assessment of individual risk beyond GA, BWt for GA and breast milk exposure e.g based on GWAS

- There may be difficulty because of lack of equipoise around interventions that act through modifying the microbiome arising from a number of very emotive published meta-analyses and reviews.

Response to Breakout Question #5

- What potential biomarkers and clinical trial endpoints could be used?
  - Are adequate clinical outcome measures available? If not can they be developed?
  - Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
  - Clinical outcome measures There are problems around the objectivity of the clinical and radiological diagnosis of NEC……
  - Appropriate intermediate end-points might be duration of parenteral nutrition dependence, discharge from hospital.
  - Biomarkers: We are not aware of any that are 'regulatory ready'
    - Possibilities being investigated include:
    - Volatile organic compounds (Ewer, Birmingham, UK)
    - Metabolomics – stool water (Modi, Imperial, UK)
    - Bile acid variability in stools (Halpern, Tucson, Arizona)

Response to Breakout Question #6

- What long-term outcome measures are available to assess the safety and efficacy of the therapy?

- Neurodevelopment
- Despite >20 published trials there is a lack of long-term outcome data for probiotic/prebiotic interventions; studies should include measures of childhood general health including particularly atopic disease and more detailed functional measures of development of immune function, energy harvesting and metabolism .

Response to Breakout Question #7

- In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach the prevention or treatment of NEC?

- Incomplete understanding of the fundamental developmental biology underpinning the pathogenesis…. Lack of understanding of the interplay between the genome, enteral nutrition…. HMO profile, the developing microbiome and immunological function in the preterm baby…..

- Individual assessment of risk

- For probiotic trials the effects on control infants and others within the nursery and modification of the microbiological environment over time –important for interpretation of trial results but for determining safety – the effects of a probiotic intervention might change over time……

DETAILED RESPONSES: Proposed projects 1

1. Development of robust case definition for surveillance and as a trial outcome…. *Data forthcoming from population based study, Modi et al.*
2. Critical review of available animal models
3. Longitudinal studies in the preterm population of the genome, microbiome, metabolomic profiles functional immunological function: defining the relationships and the associations with the occurrence of NEC, also differences from term babies : **the ontogeny of intestinal immune development.** Not only would this hugely increase understanding of the nature of the disease but it would facilitate assessment of individual risk.

DETAILED RESPONSES: Proposed projects 2

4. Spread of administered probiotic strains to non-treated infants and changes of patterns of colonisation over time
5. Coordinated programmes of trials to optimise enteral feeding: early colostrum, place of donor milk, rate of increase of feeds, fortification etc etc…..
6. Harmonisation of population based datasets, accurate recording of medications, feeding and clinical outcomes to explore associations

DETAILED RESPONSES: SUMMARY

- NEC is a major problem, prevention is urgently needed
- We are not ready to embark on large preventative trials
- BUT we have the tools to improve the basic science and establish the platform for designing future trials
- Success is dependent on multi-disciplinary, international collaboration such as this consortium.