SIGNEC and the Third International Conference on Necrotising Enterocolitis

The SIGNEC third international conference on necrotising enterocolitis, held in London in September 2015.

Introduction

SIGNEC UK was established as a special interest group for necrotising enterocolitis (NEC) by Professor Minesh Khashu to help advance a field of neonatal medicine that is poorly understood. NEC continues to be the major cause of mortality and morbidity for preterm infants. SIGNEC provides a platform for involvement of a wide range of healthcare professionals to facilitate knowledge sharing, networking and collaboration for optimising research and improvements in practice. Initially comprising health-care professionals from the UK, the group now has international involvement and includes neonatologists, paediatricians, surgeons, transfusion medicine specialists, epidemiologists, basic science researchers, nurses, dietitians, trainees and other healthcare professionals, as well as parent representatives with an interest in NEC and healthcare improvement.

The third SIGNEC international conference was held in London on 21-22 September 2015. As in previous years,[1,2] the conference saw distinguished clinicians and researchers from the USA, Canada, the UK and Europe consider NEC in great breadth and depth. Speakers discussed breakthroughs in cutting edge science (eg the role of the Paneth cell and epidermal growth factor in NEC pathogenesis, synthetic amniotic fluid, an artificial intestine); exciting developments that may result in earlier diagnosis (measurement of volatile organic compounds), and feeding and NEC (disease precipitated by a change of feeds, protection through the use of donor breast milk, lack of evidence regarding the role of osmolality in NEC and the use of probiotics).

The lack of major changes to practice over the years was highlighted by Dr Alan Fenton, President of the British Association of Perinatal Medicine (BAPM), along with suggestions of what could be done to improve practice. Delegates heard from Mr Robert Hillier a parent who had a baby born at term who developed NEC, highlighting the importance of the less common presentation (10% of NEC may occur in term infants). Current hot topics were explored in lively panel discussions, in particular probiotic use and barriers to good communication and informed choice.

Is the Paneth cell the missing link to NEC?

While NEC has been recognised as a disease of premature infants for over four decades, understanding of its pathophysiology is still incomplete. Dr Steven McElroy's laboratory at the University of Iowa has noted a lack of Paneth cells and Paneth cell products following development of NEC. Using this finding, his team has developed a novel mouse model of NEC that uses Paneth cell disruption followed by bacterial dysbiosis to induce injury that is consistent with the injury, inflammation patterns, and alterations in the bacterial microbiota that are seen with clinical disease. In his talk, Dr McElroy summarised this new model and discussed how it may be used to help answer some fundamental questions regarding development of NEC.

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The pathogenesis and treatment of NEC: tales from the crypt

Professor David Hackam described how NEC is a devastating disease of premature infants involving intestinal ischaemia and necrosis resulting in systemic sepsis and death in many cases. There is increasing recognition that NEC development occurs in response to an abnormal interaction between an underdeveloped intestinal mucosa, an immature gut microbiome, non-breast milk feeds, and a variety of ill-defined environmental and genetic factors. In seeking to understand the causes of NEC with an eye to the development of novel therapies, Professor Hackam's team has identified that the premature bowel is characterised by significantly elevated expression of Toll-like receptor 4 (TLR4) in the intestinal mucosa, and that TLR4 activation by gut microbes present in infants with NEC leads to mucosal injury and impaired repair processes. The reason for the elevated TLR4 expression in the lining of the premature infant intestine reflects the role played by TLR4 in the regulation of normal intestinal development; the developmental role switches to a pathological role in the postnatal period upon encountering microbes.

Recent studies have shown that TLR4 activation in the premature host intestine leads to NEC through direct injury to the gut stem cells, rendering the host intestine further vulnerable to disruption. The degree of gut injury is further modified by a variety of genetic factors, including the expression of TLR9 and environmental factors including the presence of hypoxia. By understanding how these various pathological processes intersect, the team has begun developing novel infant nutritive milks and a synthetic amniotic fluid that could promote the health and wellbeing of premature infants by disrupting pathological signalling downstream of TLR4. The development of an artificial intestine that harnesses the restorative power of stem cells could provide an important therapeutic approach for infants lacking a sufficient viable intestine of their own.

Strategies to modulate intestinal inflammation and repair

In her presentation, Dr Misty Good highlighted the findings of her research on the cellular and molecular mechanisms involved in the pathogenesis of NEC. Since NEC does not occur *in utero*, Dr Good sought to evaluate whether amniotic fluid provided a protective role against NEC. Specifically, she discussed how amniotic fluid inhibits pro-inflammatory signalling of the innate immune receptor, TLR4, in the fetal and neonatal intestine, and protects against NEC in small and large animal models.

Additionally, Dr Good described her recent studies elucidating

Day 1: Basic science and laboratory research	
Dr Steven J McElroy *Assistant Professor, University of Iowa, USA*	Is the Paneth cell the missing link to NEC?
Professor David J. Hackam *Chief of Pediatric Surgery, John Hopkins Children's Center, USA*	New cells on the block in the pathogenesis and treatment of NEC: tales from the crypt
Dr Misty Good *Assistant Professor of Pediatrics, University of Pittsburgh School of Medicine, USA*	Strategies to modulate intestinal inflammation and repair in the pathogenesis of NEC
Dr Alan Fenton *Consultant Neonatologist, Royal Victoria Infirmary, UK*	NEC: improving clinical practice
Professor Boris W. Kramer *Professor of Experimental Perinatology, Maastricht UMC, Netherlands*	New insights and interventions to prevent NEC: the electronic nose detects changes in the microbiome and predicts NEC
Professor Andy Ewer *Professor of Neonatal Medicine, University of Birmingham, UK*	The DOVE study: the role of volatile organic compounds in the diagnosis of NEC
Day 2: NEC: Clinical research and improvements in practice	
Mark Duman *Non-Executive Director, Patient Information Forum; Director, Monmouth Partners, UK*	Seeing parents and carers as assets: caring and coaching
Dr Sharon Unger *Medical Director, Rogers Hixon Ontario Human Milk Bank; Staff Neonatologist, Mount Sinai Hospital, Toronto, Canada*	Use of human donor milk for very low birthweight babies
Mr David Burge *Consultant Paediatric and Neonatal Surgeon, University Hospital Southampton, UK*	Is NEC requiring surgery precipitated by a change in feeds? Observations from 50 consecutive cases
Professor Kate Costeloe *Professor of Paediatrics, Barts and the London School of Medicine and Dentistry, UK*	The PiPS trial
Debbie Sandford *Chief Operating Officer and Schwartz Programme Director, The Point of Care Foundation, UK*	Schwartz rounds: a multidisciplinary approach to supporting staff
Dr Syed Mohinuddin *Consultant Neonatologist, London Neonatal Transfer Service, Barts Health NHS Trust, UK*	Bridging the knowledge-application gap: the NeoMate app
Dr Inga D. Teller *Senior Scientist, Early Life Nutrition, Nutricia Research, Netherlands*	Current scientific knowledge for the role of osmolality in the development of NEC
Panel discussions	1. Probiotics: where do we go from here? 2. Barriers to good communication and informed choice

TABLE 1 Programme of speakers.

the mechanism by which breast milk provides protection against NEC. She demonstrated how one component of breast milk, epidermal growth factor (EGF), may afford protection. EGF activates its receptor, EGFR, and inhibits TLR4 signalling leading to decreased intestinal cell death and enhanced intestinal mucosal healing in a small animal model of NEC. The importance of encouraging mothers to provide breast milk for their premature infant was highlighted.

New insights and interventions to prevent NEC: the electronic nose detects changes in the microbiome and predicts NEC

In his talk, Professor Boris Kramer reminded the audience that preterm delivery is frequently associated with microbial invasion by bacteria and/or viruses of the amniotic cavity (chorioamnionitis). In contrast to a relatively asymptomatic mother, the fetus may suffer from a fetal inflammatory response including umbilical inflammation and increased serum levels of inflammatory cytokines. Antenatal exposure to inflammation places an extremely immature neonate at high risk for adverse gastrointestinal outcomes such as NEC.

Infants who develop NEC have changes in the microbiome that precede the development of disease and have a low percentage of regulatory T lymphocytes, which are crucial for the control of inflammation. Professor Kramer's team studied the role of the immune system in the course of the chorioamnionitis in an experimental model. Chorioamnionitis was induced by ultrasound-guided, intra-amniotic injection of lipopolysaccharide from *E. coli* or *Ureaplasma urealyticum*, causing inflammation, and subsequent injury and impaired development (villus injury and altered distribution of the different intestinal epithelial lineages). The administration of interleukin-1 receptor antagonist (anakinra) ameliorated the development and inflammatory response in the fetal gut. In a second approach, systemic administration of interleukin-2 was found to reduce inflammation, prevent injury and increase the number of regulatory T cells in the fetal gut and lymph nodes.[3] In summary, the team was able to reduce inflammatory injury in the fetal gut by blocking interleukin-1 pathways or by increasing the number of circulating regulatory T lymphocytes. Immunomodulation appears to offer the possibility of interventions to prevent adverse development of the gut *in utero*.

Professor Kramer went on to discuss the analysis of metabolic activity in the fetal gut and how this may be of use in detecting patients at high risk for NEC, distinguishing them from patients at risk for sepsis. In order to assess the metabolic changes in the microbiome of preterm infants, an electronic 'nose' was used to detect volatile organic compounds (VOCs) in faecal samples; changes could be detected in infants two days before the development of NEC or sepsis, with the possibility to distinguish NEC and sepsis from each other.[4]

The DOVE study: the role of VOCs in the diagnosis of NEC

Continuing along the theme of VOCs, Professor Andy Ewer explained how their levels in biofluids might reflect changes in body state caused by disease. Faecal VOC profiles are diagnostic in certain gastrointestinal conditions and preliminary evidence suggests that the same may be true in infants with NEC.

Professor Ewer presented results from the recent case-controlled DOVE study (Diagnostic test of Organic Volatiles in necrotising Enterocolitis), which recruited 1,326 preterm infants born at 23-34 weeks' gestation from eight neonatal units. Stool samples were collected prospectively and the VOC profile of infants who developed NEC were compared with controls using gas chromatography/mass spectrometry and a bespoke sensor (called an odoreader).

Professor Kate Costeloe and Dr Misty Good.

Robert Hillier (parent).

There were 49 cases of NEC and 34 had adequate samples for analysis. Preliminary results of the VOC profiles in NEC/non-NEC cases reveal that changes in the VOC profile could be used to predict NEC up to six days before the onset of disease. Future work may include screening using a wider range of compounds.

Seeing parents and carers as assets: caring and coaching

In the first presentation of day 2, Mark Duman of the Patient Information Forum spoke about the most underutilised resource in health care: patients, parents and carers. A review of the NHS conducted in 2002 showed that a 'fully engaged public' (ie people taking more of a role in prevention and/or treatment of disease) would result in a £30 billion saving. More recent work illustrates that these 'activated patients' save between 8-21% of provider costs – a greater impact that any drug or medical device. In addition to caring, clinicians should be trained to look at the assets that service users/carers each possess. He emphasised that information and support play a key role in enabling service users to take on roles, which, like any therapy, should be tailored to meet their particular needs. Better utilisation of parents and carers of babies with NEC will improve outcomes and experiences.

Use of human donor milk for very low birthweight babies

Dr Sharon Unger shared the results from an exciting research trial in Canada, which suggests that donor breast milk is protective against NEC. Her group is planning further work including developments with regard to optimising human donor breast milk banking.

Is NEC requiring surgery precipitated by a change in feeds?

Paediatric Surgeon Mr David Burge explained how, in a review of 55 preterm infants with surgical NEC, it was noted that presentation had occurred within seven days of first exposure to non-breast milk feeds in 50% of cases, often after some weeks of stability on breast feeds. The possibility that non-IgE mediated cows' milk protein (CMP) allergy may be a significant cause of NEC was also raised. Specific case analyses, other neonatal surgical scenarios and reference to clinical and basic science publications in the literature support this mechanism. Mr Burge proposed that this concept may offer opportunities to prevent NEC by avoidance of CMP-containing feeds in at-risk infants.

The PiPS trial: early *B. breve* BBG to prevent NEC, late onset sepsis and death

Controversy remains around the routine use of probiotics for preterm babies and recommendations supporting their use rely on meta-analyses of trials employing a range of products and designs.

BAPM President Dr Alan Fenton.

Conference organiser Professor Minesh Khashu (right) with Professor Boris Kramer.

Professor Kate Costeloe described how PiPS (Probiotic in Preterm babies Study) aimed to overcome these problems by recruiting an unselected high-risk population and studying cross-colonisation between trial groups with sufficient numbers to give clear answers.

This randomised placebo-controlled trial studied the effect of early administration of a single probiotic strain, *Bifidobacterium breve* strain BBG-001 (*B. breve* BBG), given to an unselected group of babies at high risk of NEC and sepsis. The intervention was started at a mean age of 44 hours; 1,310 infants of <31 weeks' gestation were randomised. No adverse events related to the intervention were reported but no evidence of benefit was found. Cross colonisation with *B. breve* BBG was high but subgroup analysis suggested it did not impact on the results.[5] The microbiome is fundamental to the pathogenesis of sepsis and NEC but Professor Costeloe argued that currently there is insufficient knowledge of risk in individual infants and of which probiotic strains should be used, to either recommend routine use or to undertake further clinical trials.

Schwartz rounds: a multidisciplinary approach to supporting staff

A Schwartz round is a multidisciplinary forum designed for staff to come together to discuss and reflect on the non-clinical aspect of caring for patients, ie the emotional and social challenges associated with their jobs. The underlying premise for Schwartz rounds is that the compassion shown by staff can make all the difference to a patient's experience of care, but that in order to provide care with compassion, staff must feel supported in their work. NEC has a profound effect on families and healthcare professionals and Schwartz rounds provide a good avenue of support for staff. Debbie Sandford of the Point of Care Foundation reported that about 120 organisations in the UK are running, or setting up, Schwartz rounds.

Bridging the knowledge-application gap: the NeoMate app

Dr Syed Mohinuddin highlighted the issue of the knowledge-application gap, which can adversely impact patient care. He stressed the need for synchronising knowledge creation and application tools in the contemporary setting. Drawing from clinical experience and published evidence, he presented how simple steps performed well can improve patient safety.

NeoMate is a smart phone application aimed at clinicians working with sick neonates for the purpose of improving patient safety. It includes an infusion calculator, checklists for common neonatal emergencies and key reference material available to the user even without an internet connection. The clinical impact of the app remains to be evaluated. However, in high risk scenarios such as the transfer of an infant with NEC for surgery, use of such a resource has been reported to improve efficiency and safety.

The role of osmolality in the development of NEC

Since the American Association of Pediatrics recommended a cut-off point of 400mOsm/L in 1976, osmolality of infant feeds has been a concern as a high osmolality has been proposed as a contributing factor to NEC.

In her presentation, Dr Inga Teller described the scientific evidence on which this recommendation is built and identified the gaps for further investigation to better understand the likelihood of a link between osmolality of enteral feeds with NEC.

Evidence for mucosal damage is sparse and mostly based on non-digestible component solutions in high concentration ranges tested more than 30 years ago. There has been very little new evidence in the last 20 years and almost nothing is known of the effect of complete digestible enteral feeds that provide bioavailable nutrients in line with current intake recommendations.

Summary

The third SIGNEC international conference was attended by approximately 135 delegates including nurses, doctors, dietitians, basic science researchers, parent representatives and representatives from Bliss, all of whom reported the conference as very useful and inspiring. While some cutting-edge breakthroughs may take time to come to fruition, there are improvements to practice that can be implemented immediately by individuals and units. Professor Khashu highlighted the importance of 'small change leading to big impact' and urged all delegates to share their passion and inspiration with their teams to create a better healthcare system for newborn infants and their families.

References

1. **Khashu M.** SIGNEC U.K. and the first international conference on necrotising enterocolitis. *Infant* 2013;9:197-200.
2. **Khashu M.** SIGNEC U.K. and the second international conference on necrotising enterocolitis. *Infant* 2015;11:15-18.
3. **Nikiforou M., Vanderlocht J., Chougnet C.A. et al.** Prophylactic interleukin-2 treatment prevents fetal gut inflammation and injury in an ovine model of chorioamnionitis. *Inflamm Bowel Dis* 2015;21:2026-38.
4. **De Meij T.G., van der Schee M.P., Berkhout D.J. et al.** Early detection of necrotizing enterocolitis by fecal volatile organic compounds analysis. *J Pediatr* 2015;167:562-67.
5. **Costeloe K., Hardy P., Juszczak E. et al.** *Bifidobacterium breve* BBG-001 in very preterm infants: a randomised controlled phase 3 trial. *Lancet* 2015; DOI: http://dx.doi.org/10.1016/S0140-6736(15)01027-2.

For updates on the fourth SIGNEC conference, planned for 26-27 September 2016 at Chelsea Football Club, London, contact mineshkhashu@gmail.com