British Association of Perinatal Medicine

Research Update – May 2018

Coming soon! – There will be a section of the BAPM dedicated purely to Neonatal research. In this section of the website BAPM will try to highlight a few published studies each month that are of interest to those working in neonatology and also give some highlights of new research presented at significant neonatal conferences. Here are some highlights from presentations at the recent PAS Meeting in Toronto as highlighted on Twitter.

Twitter

First of all, a group of enthusiastic neonatologists who all use Twitter to inform others of new published research in the field met to agree hashtags which would be used to signpost others to neonatal research. It was agreed that a universal hashtag was important and that free-online content should be differentiated with a different hashtag to help identify it. The hashtags agreed were:

#NeoEBM for all evidenced based neonatal research content

#FOAMNeo for all free open access online content. FOAM = free online access to medicine and is used by some other specialities.
We will fit in with this new agreement for anything we tweet from BAPM.
If you're not on Twitter consider using it and follow **@BAPM_official** and use the hashtags above to find posts of neonatal interest.

The following were studies that others highlighted on Twitter and seem to be of particular importance. Remember that these studies are not yet published and it is important to wait for the paper to be peer reviewed and appear before fully interpreting.

1. STOP-BPD trial (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3245429/)
   More evidence that early post-natal hydrocortisone may be beneficial in terms of mortality following on from the PREMILOC study (see https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00202-6/abstract and https://jamanetwork.com/journals/jama/fullarticle/2614188). This large randomised controlled trial used targeted hydrocortisone, given for 22 days starting in the second week of life in ventilated infants < 30 weeks did not reduce the composite outcome of death or CLD (at 36 weeks) but did reduce mortality before 36 weeks PMA. This study differs from PREMILOC in that the hydrocortisone was given later and was targeted rather than used as prophylaxis when compared to PREMILOC. Unlike PREMILOC long term outcomes for this study are not yet available.

2. Sustained Aeration of Infant Lungs (SAIL) trial: Elizabeth E Foglia, et al. The SAIL trial (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4372179/). The study intervention consisted of performing an initial SI (20 cm H_20 for 15 seconds) followed by a second SI (25 cm H_2O for 15 seconds), and then

PEEP with or without IPPV, as needed. The control group were treated with initial IPPV with PEEP. The primary outcome is the combined endpoint of bronchopulmonary dysplasia or death at 36 weeks post-menstrual age.
460 infants were randomised; 426 had data available. The groups were well-balanced for maternal and infant characteristics. The trial was stopped because of an elevated risk of death within 48 hours with sustained inflation with no evidence of benefit.

3. The HUNTER trial. Brett Manley et al (http://bmjopen.bmj.com/content/7/6/e016746) is a randomised controlled, non-inferiority trial, comparing nasal high flow with nasal continuous positive airway pressure as primary support for newborn infants with early respiratory distress born in Australian non-tertiary special care nurseries. 754 infants >31 weeks were randomised to CPAP or high flow for initial respiratory support. Treatment failure was 14.5% for high flow vs 8% for CPAP. The conclusion was that CPAP was superior to high flow at preventing treatment failure when used as early respiratory support for larger preterm infants.

4. Resuscitation in context of cooling (Marianne Thoresen).
Data were presented from 8 UK hospitals 2006-2017; in infants fulfilling TOBY criteria, 12 infants had Apgar 0 & 13 infants had Apgar 1-2 at 10 minutes. Of these 25 infants with Apgar at 10 minutes of 0 to 2, 9 died and 16 survived with normal development at 2 years and no disability. The conclusion was that resuscitation should continue to at least 20-25 minutes in context of therapeutic hypothermia given an intact survival in 50% of cooled infants, who underwent prolonged resuscitation with a 10min Apgar of 0.

Neonatal papers of interest published in the last month

1. **A review of Hydrolyzed Formula Compared With Standard Formula for Preterm Infants**
JAMA. 2018;319(16):1717-1718. doi:10.1001/jama.2018.3623 from Derek Ng, Nick Embleton and Bill McGuire:

Clinical Question For preterm infants, is hydrolyzed formula associated with lower rates of feeding intolerance, lower rates of necrotizing enterocolitis, and faster rates of growth compared with standard cow's milk formula?
Bottom Line Compared with standard formula, feeding preterm infants hydrolyzed formula is not associated with a lower rate of feeding intolerance, a lower rate of necrotizing enterocolitis, or with faster growth.

2. **Neurodevelopmental Impairment among Extremely Preterm Infants in the Neonatal Research Network. Adams-Chapman et al.**
Pediatrics 2018;141(5).

Objectives: Evaluate the spectrum of neurodevelopmental outcome in a contemporary cohort of extremely preterm infants. We hypothesize that the rate of severe neurodevelopmental impairment (NDI) decreases over time.
Methods: Retrospective analysis of neurodevelopmental outcome of preterm infants ≤27 weeks' gestational age (GA) from a Neonatal Research Network center that completed neurodevelopmental follow-up assessments between April 1, 2011, and January 1, 2015. The Bayley Scales of Infant Development-III (BSID III) and a standardized neurosensory examination were performed between 18 and 26 months' adjusted age. Outcome measures were neurologic examination diagnoses, BSID III cognitive and motor scores, sensory impairment, and the composite outcome of NDI, based on the BSID III cognitive score (analyzed by using a cutoff of <85 or <70), BSID III motor score of <70, moderate or severe cerebral palsy (CP), bilateral blindness, and hearing impairment.
Results: Two thousand one hundred and thirteen infants with a mean GA of 25.0 ± 1.0 weeks and mean birth weight of 760 ± 154 g were evaluated. The 11% lost to follow-up were less likely to have private insurance, late-onset sepsis, or severe intraventricular hemorrhage. Neurologic examination results were normal in 59%, suspect abnormal in 19%, and definitely abnormal in 22%. Severe CP decreased 43% whereas mild CP increased 13% during the study. The rate of moderate to severe NDI decreased from 21% to 16% when using the BSID III cognitive cutoff of <70 (P = .07) or from 34% to 31% when using the BSID III cognitive cutoff of <85 (P = .67).
Conclusions: Extremely preterm children are at risk for NDI. Over time, the rate of moderate to severe NDI did not differ, but the rates of severe CP decreased, and mild CP increased.

3. **Neurobehavioral Outcomes 11 Years After Neonatal Caffeine Therapy for Apnea of Prematurity.**
Pediatrics. 2018 May;141(5). pii: e20174047. doi: 10.1542/peds.2017-4047. Epub 2018 Apr 11.
Mürner-Lavanchy IM, Doyle LW, Schmidt B, Roberts RS, Asztalos EV, Costantini L, Davis PG, Dewey D, D'Ilario J, Grunau RE, Moddemann D, Nelson H, Ohlsson A, Solimano A, Tin W, Anderson PJ; Caffeine for Apnea of Prematurity (CAP) Trial Group.

Abstract
Background: Caffeine is effective in the treatment of apnea of prematurity. Although caffeine therapy has a benefit on gross motor skills in school-aged children, effects on neurobehavioral outcomes are not fully understood. We aimed to investigate effects of neonatal caffeine therapy in very low birth weight (500-1250 g) infants on

neurobehavioral outcomes in 11-year-old participants of the Caffeine for Apnea of Prematurity trial.
Methods: Thirteen academic hospitals in Canada, Australia, Great Britain, and Sweden participated in this part of the 11-year follow-up of the double-blind, randomized, placebo-controlled trial. Measures of general intelligence, attention, executive function, visuomotor integration and perception, and behavior were obtained in up to 870 children. The effects of caffeine therapy were assessed by using regression models.
Results: Neurobehavioral outcomes were generally similar for both the caffeine and placebo group. The caffeine group performed better than the placebo group in fine motor coordination (mean difference [MD] = 2.9; 95% confidence interval [CI]: 0.7 to 5.1; P = .01), visuomotor integration (MD = 1.8; 95% CI: 0.0 to 3.7; P < .05), visual perception (MD = 2.0; 95% CI: 0.3 to 3.8; P = .02), and visuospatial organization (MD = 1.2; 95% CI: 0.4 to 2.0; P = .003).
Conclusions: Neonatal caffeine therapy for apnea of prematurity improved visuomotor, visuoperceptual, and visuospatial abilities at age 11 years. General intelligence, attention, and behavior were not adversely affected by caffeine, which highlights the long-term safety of caffeine therapy for apnea of prematurity in very low birth weight neonates.

4. **Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood**
   Edward Mitre, Apryl Susi, Laura E. Kropp, et al
   JAMA Pediatr. Published online April 2, 2018. doi:10.1001/jamapediatrics.2018.0315

Question Does use of medications that disturb the microbiome in infancy increase subsequent risk of developing allergic diseases?
Findings In this cohort study of 792 130 children, the hazard of developing an allergic disease was significantly increased in those who had received acid-suppressive medications or antibiotics during the first 6 months of life.
Meaning Exposure to acid-suppressive medications or antibiotics in the first 6 months of life may increase risk of allergic disease development.

Abstract
Importance Allergic diseases are prevalent in childhood. Early exposure to medications that can alter the microbiome, including acid-suppressive medications and antibiotics, may influence the likelihood of allergy.
Objective To determine whether there is an association between the use of acid-suppressive medications or antibiotics in the first 6 months of infancy and development of allergic diseases in early childhood.
Design, Setting, and Participants A retrospective cohort study was conducted in 792 130 children who were Department of Defense TRICARE beneficiaries with a birth medical record in the Military Health System database between October 1,

2001, and September 30, 2013, with continued enrollment from within 35 days of birth until at least age 1 year. Children who had an initial birth stay of greater than 7 days or were diagnosed with any of the outcome allergic conditions within the first 6 months of life were excluded from the study. Data analysis was performed from April 15, 2015, to January 4, 2018.

Exposures were defined as having any dispensed prescription for a histamine-2 receptor antagonist (H2RA), proton pump inhibitor (PPI), or antibiotic.

Main Outcomes and Measures The main outcome was allergic disease, defined as the presence of food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, urticaria, contact dermatitis, medication allergy, or other allergy.

Results Of 792 130 children (395 215 [49.9%] girls) included for analysis, 60 209 (7.6%) were prescribed an H2RA, 13 687 (1.7%) were prescribed a PPI, and 131 708 (16.6%) were prescribed an antibiotic during the first 6 months of life. Data for each child were available for a median of 4.6 years. Adjusted hazard ratios (aHRs) in children prescribed H2RAs and PPIs, respectively, were 2.18 (95% CI, 2.04-2.33) and 2.59 (95% CI, 2.25-3.00) for food allergy, 1.70 (95% CI, 1.60-1.80) and 1.84 (95% CI, 1.56-2.17) for medication allergy, 1.51 (95% CI, 1.38-1.66) and 1.45 (95% CI, 1.22-1.73) for anaphylaxis, 1.50 (95% CI, 1.46-1.54) and 1.44 (95% CI, 1.36-1.52) for allergic rhinitis, and 1.25 (95% CI, 1.21-1.29) and 1.41 (95% CI, 1.31-1.52) for asthma. The aHRs after antibiotic prescription in the first 6 months of life were 2.09 (95% CI, 2.05-2.13) for asthma, 1.75 (95% CI, 1.72-1.78) for allergic rhinitis, 1.51 (95% CI, 1.38-1.66) for anaphylaxis, and 1.42 (95% CI, 1.34-1.50) for allergic conjunctivitis.

Conclusions and Relevance This study found associations between the use of acid-suppressive medications and antibiotics during the first 6 months of infancy and subsequent development of allergic disease. Acid-suppressive medications and antibiotics should be used during infancy only in situations of clear clinical benefit.

Two papers published recently in Fetal and Neonatal Archives using data from the NDAU database which are of interest. One showing changes in mortality rates over time which are encouraging but importantly regional differences which may be important and could be the focus of future work. The second showing how long babies actually spend in our neonatal units giving some useful information which could be shared with parents about predicting time of discharge but also which could be used for future work looking at variation and reasons for this.

5. **Survival of very preterm infants admitted to neonatal care in England 2008–2014: time trends and regional variation**
   Shalini Santhakumaran et al. (http://fn.bmj.com/content/103/3/F208)

Abstract

Objective To analyse survival trends and regional variation for very preterm infants admitted to neonatal care.

Setting All neonatal units in England.
Patients Infants born at 22+0–31+6 weeks+days gestational age (GA) over 2008–2014 and admitted to neonatal care; published data for admitted infants 22+0–25+6 weeks+days GA in 1995 and 2006, and for live births at 22+0–31+6 weeks+days GA in 2013.
Methods We obtained data from the National Neonatal Research Database. We used logistic regression to model survival probability with birth weight, GA, sex, antenatal steroid exposure and multiple birth included in the risk adjustment model and calculated annual percentage change (APC) for trends using joinpoint regression. We evaluated survival over a 20-year period for infants <26 weeks' GA using additional published data from the EPICure studies.
Results We identified 50 112 eligible infants. There was an increase in survival over 2008–2014 (2008: 88.0%; 2014: 91.3%; adjusted APC 0.46% (95% CI 0.30 to 0.62) p<0.001). The greatest improvement was at 22+0–23+6 weeks (APC 6.03% (95% CI 2.47 to 3.53) p=0.002). Improvement largely occurred in London and South of England (APC: London 1.26% (95% CI 0.60 to 1.96); South of England 1.09% (95% CI 0.36 to 1.82); Midlands and East of England 0.15% (95% CI −0.56 to 0.86); and North of England 0.26% (95% CI −0.54 to 1.07)). Survival at the earliest gestations improved at a similar rate over 1995–2014 (22+0–25+6 weeks, APC 2.73% (95% CI 2.35 to 3.12), p value for change=0.25).
Conclusions Continued national improvement in the survival of very preterm admissions masks important regional variation. Timely assessment of preterm survival is feasible using electronic records.

6. **Estimating neonatal length of stay for babies born very preterm**
   Sarah E Seaton et al (http://fn.bmj.com/content/early/2018/03/27/archdischild-2017-314405)

Abstract
Objective To predict length of stay in neonatal care for all admissions of very preterm singleton babies.
Setting All neonatal units in England.
Patients Singleton babies born at 24–31 weeks gestational age from 2011 to 2014. Data were extracted from the National Neonatal Research Database.
Methods Competing risks methods were used to investigate the competing outcomes of death in neonatal care or discharge from the neonatal unit. The occurrence of one event prevents the other from occurring. This approach can be used to estimate the percentage of babies alive, or who have been discharged, over time.
Results A total of 20 571 very preterm babies were included. In the competing risks model, gestational age was adjusted for as a time-varying covariate, allowing the difference between weeks of gestational age to vary over time. The predicted percentage of death or discharge from the neonatal unit were estimated and presented graphically by week of gestational age. From these percentages,

estimates of length of stay are provided as the number of days following birth and corrected gestational age at discharge.

Conclusions These results can be used in the counselling of parents about length of stay and the risk of mortality.