Nordic Neonatal Meeting News 2021

PRESENTATIONS FROM THE 10th NORDIC NEONATAL MEETING, 18–19 NOVEMBER 2021, STOCKHOLM, SWEDEN

The Nordic Neonatal Meeting celebrated its 10th anniversary on 18–19 November 2021, by hosting a hybrid gathering of attendees both in person in Stockholm and online. This year's presentation themes included long-term follow-up on neurodevelopmental outcomes and management of BPD, together with a survey on discharge readiness criteria and updates on ongoing clinical studies in Nordic centres.

Acknowledgements

Scientific Committee: Lars Björklund (Sweden), Christian Heiring (Denmark), Baldvin Jónsson (Sweden), Claus Klingenberg (Norway), Liisa Lehtonen (Finland), Marjo Metsäranta (Finland), Jesper Padkær Petersen (Denmark), Ola D Saugstad (Norway)

Sponsor: Chiesi Pharma AB, Sweden

Long term neurobehavioural outcomes

Professor Neil Marlow, University College London, United Kingdom

Extremely premature babies born today survive a good deal longer than 20 years ago; however, although increased focus on brain-oriented neonatal care in this period has had a beneficial effect on the rates of GMH and CP,[1] there has been little improvement in the proportion of children affected by severe disabilities.[2,3] In the opening session of the 10th NNM, Professor Neil Marlow from University College London highlighted how the early trauma of extremely premature birth can result in cognitive and behavioural impairments that continue to pose a challenge into adult life. A recent meta-analysis including more than 2,000 participants showed that adults born very preterm (before 32 weeks' GA or very low birthweight) had significantly lower IQ compared with adults born at term, the most immature cohorts having the greatest deficits. In the EPICURE study there was no sign of IQ recovery or catch-up among 315 children born before 26 weeks' GA, at the age of 19 years *(Figure 1)*.[4] Similarly, there was no sign of catch-up in the behavioural trajectories *(Figure 2)*, suggesting that extremely preterm birth is associated with fixed deficits that do not improve with age.[5]

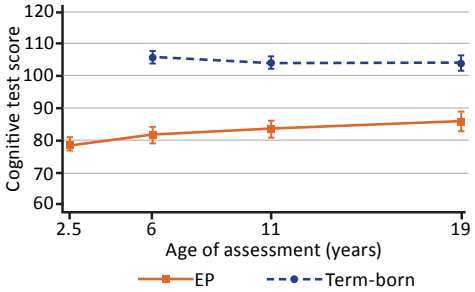


Figure 1. Stability of IQ across childhood. Reproduced from Linsell et al, 2018.[4]

Abbreviations

BAPQ	Broader Autism Phenotype Questionnaire	FNC	functional network connectivity	NAIS	neonatal arterial ischemic stroke
BDP	bronchopulmonary dysplasia	GA	gestational age	NICU	neonatal intensive care unit
CI	confidence interval	GMH	germinal matrix haemorrhage	OR	odds ratio
CP	cerebral palsy	ILCOR	International Liaison Committee on Resuscitation	PPV	positive pressure ventilation
CPAP	continuous positive airway pressure	IVH	intraventricular haemorrhage	VPT	very preterm
ERC	European Resuscitation Council			WHO	World Health Organization

Another outcome that has generated scientific interest in recent years is the prevalence of social communication disorders, including autism. In another recent analysis from the EPICURE study, young adults born before 26 weeks' GA scored significantly higher on the BAPQ tool compared with controls, including on the subscales for aloof or rigid personality and pragmatic language *(Figure 3)*.[6] Young adults born extremely preterm also had lower scores for empathy, and at the age of 19, 10% reported having been diagnosed with autism compared with only 1.6% of controls.[6] This data concurs with a Norwegian study from 2008 which reported a dramatically increased risk of being diagnosed with autism in adulthood among individuals born before 32 weeks' GA compared with those born at term.[7] In Professor Marlow's opinion, these findings reflect the neurological injuries and developmental changes that follow extremely preterm birth. The EPICURE investigators have also shown that young adults born extremely preterm – especially those living with neurodevelopmental impairment – and their families tend to have poorer quality of life compared with controls born at term, again reflecting the functional impact of these problems.[8]

In addition to the long-term cognitive and behavioural consequences of extremely preterm birth in adulthood, Professor Marlow also highlighted outcomes in a more global perspective of functioning and performance. The WHO has developed an International Classification of Functioning Disability and Health Children and Youth (ICF-CY) which measures functioning and participation in young people up to the age of 19 years at three levels (optimal, at risk or challenged) in five domains (cognition, executive function, self-care, academic achievement and social participation). Although the proportion of individuals achieving an overall status of 'functioning optimally' was not hugely different among 17-year-olds born prematurely compared with those born at term, the former group had a much higher prevalence of "challenged" status on all domains.[9] Male sex and low socioeconomic status were associated with higher risk of poor functional outcomes. These findings reflect data from the United States which shows that the odds ratios for substance abuse, contact with the police, and having sexual intercourse or giving birth at the age of 22 years were significantly lower in a cohort of 242 individuals with very low birth weight and born at a mean GA of 30 weeks, compared with controls born at term.[10] Professor Marlow described how this report, when first published, found its way into the general media and was hailed as portraying "model citizens"; however, far from this being the case, it rather reflects a social and behavioural profile of internalising and having little contact with peer groups, thus avoiding any risk-taking behaviour. More recently, data from Canada has linked extremely low birth weight and preterm birth with having a lower income, more health problems and lower self-esteem in the fourth decade of life, as well as lower odds of full-time employment or having a family, and higher odds of being on social benefits.[11]

Professor Marlow concluded his presentation by reminding the NNM audience that the long-term adverse effects on mental health and cognitive function are only some of the implications of extremely preterm birth in adult life. In his view, the pervasive effects of the arrest of developmental progress in normal foetal life together with the trauma of interventions in the NICU will likely result in a wide spectrum of very long-term outcomes that should give cause for concern, not only for paediatricians but also for clinicians caring for adult patients. Efforts to better understand ageing after extremely preterm birth and the adoption of a long view in clinical practice will be key to supporting these individuals in the future.

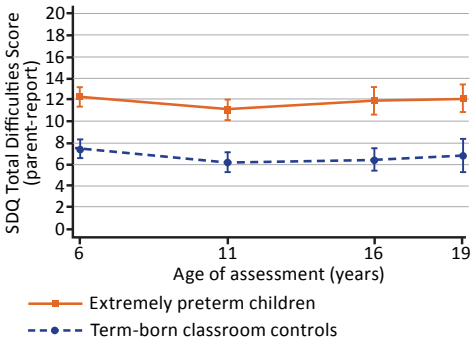


Figure 2. Stability of behavioural problems across childhood. Reproduced from Linsell et al, 2019.[5]

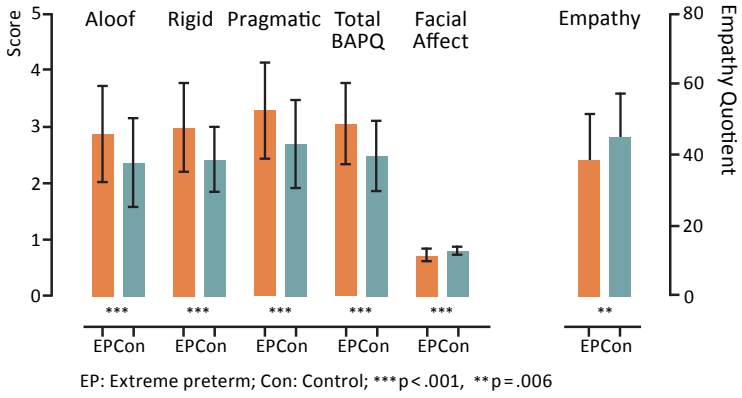


Figure 3. Scores on measures of autistic traits and empathy at 19 years. Adapted from O'Reilly et al, 2021.[6]

Follow up of high-risk neonates in Sweden

Clinicians might be forgiven for thinking that the very high quality of paediatric healthcare in the Nordic countries may render follow-up of babies and children born prematurely redundant. However, as Professor Ulrika Ådén from Karolinska University Hospital in Stockholm pointed out in her presentation at NNM 2021, early identification of some of the health issues that may affect individuals born extremely preterm may pose a challenge in the outpatient setting. This together with an increasing commitment to responsive caregiving as outlined by the WHO,[12] plus survey data showing that almost one in five families feel the care they received after discharge was only poor or fair,[13] suggests that there is a need for structured neonatal follow-up in this setting. The Swedish Neonatal Quality Register (SNQ) was established in 2015 and aim to include all high-risk neonates – including those born before 28 weeks' GA, small for GA by more than three standard deviations, or with other critical illnesses at the discretion of the physician – for structured follow-up during the first two years of life and when starting school, with a view to providing early support and relevant referrals as well as collecting data for long-term follow-up. The latest annual report from the SNQ shows that the majority of the Swedish healthcare regions are close to attaining the inclusion target of 90% of eligible children; of a total of just over 1,505 children registered, just over a third had been referred during the first two years of follow-up, mainly for language delays and neurodevelopmental disorders.

The finding in the EPICURE study that improved survival after extremely pre-

Professor Ulrika Ådén, Karolinska University Hospital, Stockholm, Sweden

term birth has not been accompanied by a reduction in neurodevelopmental impairment[3] is borne out by data from the Swedish EXPRESS cohorts. While a modest improvement could be seen in survival rates without major neonatal morbidity during the first two years of follow-up between the first EXPRESS research study in 2004–2007 and the EXPRESS 2 registry cohort in 2014–2016,[14] no improvement was seen in the rate of neurodevelopmental impairments according to preliminary data. A range of neurodevelopmental impairments, including CP and autism, were not detected until the six-year follow-up at the time of starting school.[15] With the help of the EXPRESS cohorts, Professor Ådén and her team at Karolinska have been able to link MRI changes, and markers of variable brain development such as motor problems, to impaired neurodevelopmental outcomes after extremely premature birth.[16–21] Some of these findings have been applied in the development of targeted interventions, such as singing kangaroo care to promote auditory and speech development,[22] and the Stockholm Preterm Interaction-Based Intervention (SPIBI) which is designed to enhance parent-child interaction,[23] which in turn has been shown to improve school-age outcomes.[24] Professor Ådén's take-home message was that although neonatal care has come a long way in terms of improving morbidity-free survival after extremely preterm birth, there is still a long way to go, and more research is needed in this field.

The PIPARI study: behavioural features and mental health of adolescents born preterm

Dr Katri Lahti, Turku University Hospital, Finland

Dr Sirkku Setänen, Turku University Hospital, Finland

The PIPARI study (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) is a prospective, longitudinal cohort study designed to follow a cohort of infants born VPT (between 28 and 32 weeks' GA) in Turku University Hospital between 2001 and 2006, from the perinatal period until adulthood. The scientific programme at NNM 2021 included two presentations of data from recent follow-up assessments of neuropsychological development among adolescent PIPARI participants.

Dr Katri Lahti performed resting-state functional MRI scanning of adolescents born VPT and term-born controls at the age of 13 years, to visualise study brain maturation and connectivity differences.[25] Analyses of the time spent in each clustered functional network connectivity (FNC) state showed that adolescents born VPT spent significantly longer time in the hypoactive state compared with controls. Meta-state metrics showed that the VPT group occupied fewer connectivity states and made fewer switches, with a narrower mean span and shorter distance travelled between occupied states during the scan. Dr Lahti and her colleagues observed that the MRI findings in the VPT group of longer dwell time in the least connected state and significantly fewer meta-state changes were similar to what has been seen in autism spectrum disorder (ASD),[26] and concluded that individuals born VPT remain vulnerable to neuropsychiatric morbidity 13 years after birth.

In the second analysis from the PIPARI study, Dr Sirkku Setänen showed the results of mental health assessments performed at the age of 17 years, to explore the association between VPT birth and the prevalence of depression and anxiety. This analysis included a total of 62 adolescents born VPT and 79 term-born controls, who completed a modification of the Beck Depression Inventory (RBDI)[27] and the Overall Anxiety and Impairment Scale (OASIS).[28] The results indicated a non-significant trend towards more depressive symptoms among female adolescents born VPT compared with controls *(Table 1)*, which Dr Setänen speculated could reach significance as the PIPARI cohort continues to mature. There was no difference between male adolescents born VPT and controls with respect to depressive symptoms; nor was the prevalence of anxiety higher among adolescents born VPT. Recently published registry data has shown significantly higher odds ratios for depression among individuals born before 28 weeks' GA,[29] and the suggestion of a higher risk of depression among adolescents born VPT in the PIPARI study would be consistent with this finding.

	Females			Males		
	Very preterm group, n=33	Control group, n=49	p	Very preterm group, n=28	Control group, n=27	p
RBDI total, median (min, max)	2.0 (0.0, 10.0), data missing for one adolescent	1.0 (0.0, 18.0)	0.06	0.0 (0.0, 9.0)	0.0 (0.0, 20.0)	0.4
OASIS total, median (min, max)	4.0 (0.0, 14.0)	4.0 (0.0, 13.0)	0.5	3.0 (0.0, 14.0)	2.0 (0.0, 14.0)	0.2

Table 1. Depression and anxiety in adolescents born VPT and term-born controls. Reproduced with permission from the speaker.

Discharge of the very preterm born infant to home: Nordic survey

Dr Sofia Arwehed, Uppsala University Hospital, Sweden

A survey among NICUs in the Nordic countries has become something of a fixture at the NNM meetings, to map current practice and highlight any prominent differences. For NNM 2021, Dr Sofia Arwehed from Uppsala University Hospital conducted a survey into routines and criteria for discharging very preterm-born infants from the NICU to be cared for by the parents at home. The survey was sent in digital format to 102 NICUs in Denmark, Finland, Norway and Sweden and achieved a response rate of 64% with an even geographical distribution and roughly equal representation of Level II and Level III units.

One half of the responding units have written guidelines and/or criteria in place for discharge of very preterm-born infants, which mainly focus on respiratory assessment but also include criteria for feeding skills and weight gain, thermoregulation and parental competence. Written criteria for socially-related matters are less common, but most responding units reported applying such criteria to some degree in routine clini-

cal practice. The age at which the discharge criteria are applied is either 34 weeks' (55% of units) or 35 weeks' (45%) post-menstrual age (PMA). Respiratory readiness for discharge is mostly determined by clinical assessment; structural assessments with ECG and pulse oximetry are used in some units. Notably, fewer than half of the units involve the parents in their clinical assessments. Most units require infants to be stable without caffeine for discharge, for a mean duration of three days (range one to eight days). The thermoregulation criterion is defined in most centres as the infant's ability to sustain normal body temperature without a heating mattress. Nutritionally, the main criterion for an infant being ready for discharge is steady weight gain in most units, with one notable exception: units in Finland more often apply the criterion of reaching a certain weight to be ready for discharge (most commonly 2,000g). Dr Arwehed stressed that this was the only survey question where there was a significant difference between the Nordic countries. Several of the responding units also apply criteria for bottle- or breastfeeding skills, and more than half of the respondents agree with the statement that "early discharge promotes breastfeeding." The most common social criterion applied in assessing readiness for discharge is the parents' ability to communicate either in the local language or in English. As Dr Arwehed pointed out, "the parents' ability to understand information and give feedback is part of the nurse's or physician's evaluation, as this will affect our ability to estimate the readiness for discharge."

In terms of planning and executing the discharge process itself, three out of four units will broach the subject of discharge before term age with the family antenatally or within the first week after a preterm birth. The detailed planning, which involves providing the parents with extensive information and education, typically kicks in at around one to two weeks before discharge. Most units allow for readmission after discharge, although many reported that readmissions rarely happen. Once a VPT-born infant has been discharged and is cared for by the parents at home, many units extend the NICU support chain to include home care visits, mainly by registered nurses, and around half of the units offer digital follow-up contacts via video calls. Almost 90% of respondents agreed or strongly agreed with the statement that "home is the best place for respiratory- and circulatory-stable preterm-born infants to grow and develop." In Dr Arwehed's opinion, early discharge of VPT-born infants can play an important role in promoting parental empowerment in terms of caring for and understanding the infant's needs, and the process should be facilitated by providing optimised homecare in cooperation with the parents.

The parents' ability to understand information and give feedback is part of the nurse's or physician's evaluation, as this will affect our ability to estimate the readiness for discharge.

Early prediction of cerebral palsy – from clinical observation to AI

Professor Ragnhild Støen, St Olav's Hospital /NTNU, Trondheim, Norway

CP affects one in every 500 live births which is equivalent to 17 million children worldwide, making CP the most common physical disability to affect children. Preterm-born infants are at increased risk of developing CP as a consequence of injury to the developing brain, ranging from a 1/40 risk among infants born before 28 weeks' GA, to a 1/3 risk among infants admitted to NICU with NAIS. However, as Professor Ragnhild Støen from Trondheim highlighted in a scientific presentation at NNM 2021, despite the perinatal origin of the brain injury, the diagnosis of CP is often delayed, resulting in delayed access to early interventions and appropriate follow-up approaches. The general movement assessment (GMA), in which infants' spontaneous movements are observed to detect reduced or absent features such as fidgety movements, has been shown to predict the risk of developing CP with high levels of sensitivity and specificity, and can be used as early as at the age of three months, providing a window of opportunity for early interventions.[30,31] Evidence-based guidelines published in 2017 recommend GMA as the most accurate method for early identification of CP, especially in combination with imaging.[32]

As a diagnostic tool, GMA relies on consistent evaluations by highly trained expert observers. To further increase the predictive accuracy, a team of researchers at Professor Støen's centre has developed a method for predicting the risk of developing CP based on computerised analysis of video recordings using artificial intelligence. The team used markerless motion tracking to capture 20,000 poses from more than 1,400 video recordings of infants, which were then annotated by expert observers.[33] The annotated recordings were used to train the deep-learning-based CP prediction method *(Figure 1)*.[34,35] The method was validated and tested in two data sets of a total of 557 infants deemed at high risk of CP in four centres in the United States, Norway, Belgium and India; external validation showed that the deep-learning-based prediction method could identify infants at risk of developing CP with higher predictive accuracy than expert observation (manuscript in preparation). The investigators are currently seeking industrial sponsors for additional studies; meanwhile, the method is undergoing feasibility testing in clinical practice, to gauge its utility as a screening tool for selecting infants for GMA, or potentially a complete alternative to GMA.

Figure 1. Motion tracking of poses (a) and annotated model (b). Reproduced from Groos et al, 2022.[36]

Management of severe BPD and pulmonary hypertension

Professor Leif Nelin, Nationwide Children's Hospital, Columbus, Ohio, USA

Since BPD was first described in 1967, the term has evolved from describing a condition of ventilator-induced lung injury observed in infants born at 33 or 34 weeks' GA with surfactant deficiency,[37] to encompassing a wide spectrum of neonatal lung disease occurring in very preterm-born infants as a consequence of abnormal lung development.[38] In two back-to-back keynote presentations at NNM 2021, Professor Leif Nelin from the Nationwide Children's Hospital in Columbus, Ohio highlighted some of the challenges and unmet needs in the clinical management of severe BPD, especially in terms of optimising neurodevelopmental outcomes, and managing complications such as pulmonary hypertension.

Professor Nelin began by pointing out that although the pathogenesis behind BPD is fairly well understood – it is a process that begins at the time of conception with pregnancy abnormalities and exposures affecting foetal lung development, and the acute injury associated with preterm birth and neonatal care progressing to chronic lung injury with repair and remodelling over months and years[39] – the condition itself remains poorly defined and therefore difficult to identify objectively. The Nationwide Children's Hospital has adopted the recent criteria proposed by the Neonatal Research Network (NRN), which classifies BPD based on respiratory support at 36 weeks' postmenstrual age as either Grade 1 (requiring supplemental oxygen only), Grade 2 (requiring non-invasive respiratory support in the form of continuous positive airway pressure [CPAP], nasal intermittent positive pressure ventilation [nIPPV] or high-flow nasal cannula [HFNC]), or Grade 3 (requiring invasive respiratory support with IPPV).[38] These criteria have been shown to predict adverse outcomes in infants, including death, serious respiratory morbidity, and neurodevelopmental impairment (NDI).[38] The lung function impairment resulting from BPD in infancy marks the beginning of a downward trajectory, with lung function worsening over time during childhood *(Figure 1)*[40] and into adulthood,[41,42] making BPD a life-long health problem.

The association between BPD and NDI is thought to reflect BPD as a marker of overall illness, as well as the fact that it is also associated with poor prognostic indicators such as growth failure and prolonged hospitalisation, and that the physiological changes induced by BPD due to hypoxia, inflammation and acidosis are known to cause abnormal development. An additional hypothesis for why BPD may contribute to neurodevelopmental sequelae is that the standard treatment protocol for BPD in the NICU is developmentally inappropriate, as it is based on an "acute care" model which emphasises rapid weaning and frequent changes in care,[43,44] whereas BPD is a chronic illness that requires a chronic, multidisciplinary approach to care both in the NICU and outpatient settings.[44,45] At the Nationwide Children's Hospital, BPD care relies on the basic principles of avoiding infection and cor pulmonale, providing superb nutrition and chronic-phase ventilation, and also providing extraordinary developmental care which ensures that developmental milestones can be attained despite the severe illness, instead of being put on hold until the patient has recovered.[46,47] Not only has this approach

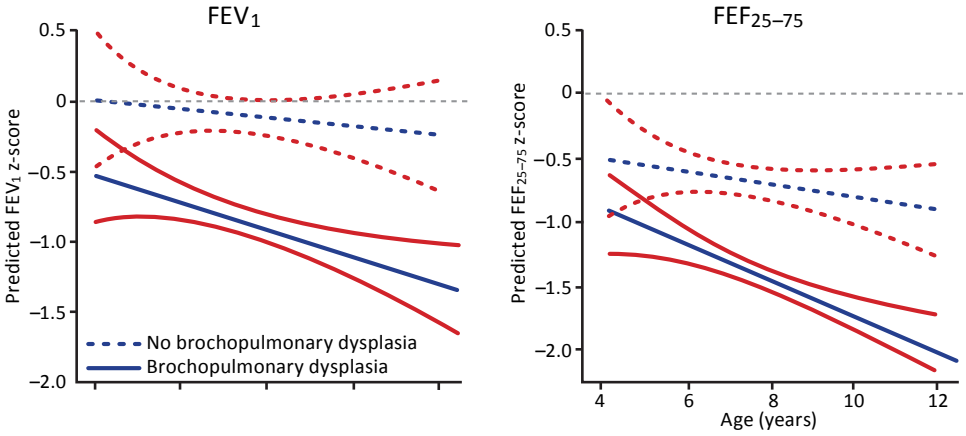


Figure 1. Lung function in children with and without BDP. Reproduced from Simpson et al, 2018.[40]

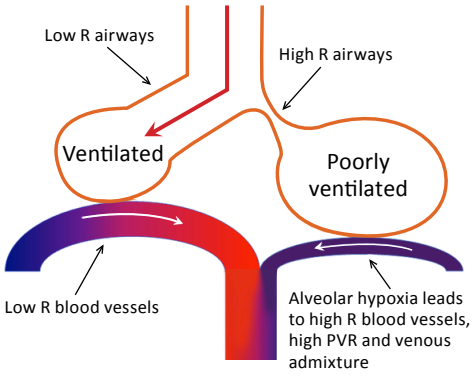


Figure 2. V/Q mismatch in PH. Reproduced with permission from the speaker.

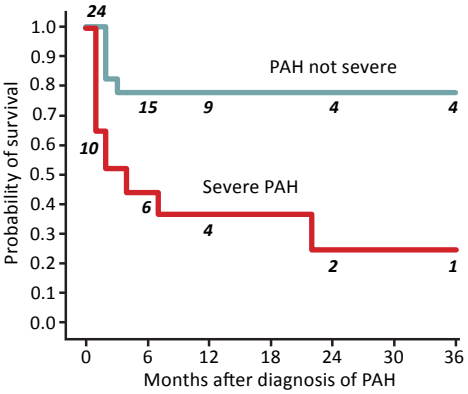


Figure 3. Probability of survival for patients with BPD and pulmonary arterial hypertension (PAH) by severity. Reproduced from Khemani et al, 2007. [55]

resulted in the Nationwide Children's Hospital having lower BPD-related mortality than most other NICUs in the US, as shown in the Children's Hospitals Neonatal Consortium database (CHND); in addition, more than half of infants at the centre with moderate to severe BPD had no NDI.[48]

Pulmonary hypertension (PH) is a common and often serious co-morbidity in BPD. PH develops as a consequence of pulmonary vascular remodelling arising from lung injury associated with preterm birth, with thickening of the arterial walls and luminal narrowing increasing the vascular resistance in the lungs and causing increased pulmonary pressure and right ventricular afterload.[49–52] Professor Nelin reminded the NNM audience that PH is often caused by a ventilation-perfusion (V/Q) mismatch, where the well-ventilated part of the lung will have low resistance and normal blood flow, unlike poorly ventilated parts where alveolar hypoxia will lead to high pulmonary vascular resistance (PVR) and venous admixture *(Figure 2)*. Echocardiography is the primary method of diagnosing PH in infants with BPD, for whom cardiac catheterisation is often not feasible. The reported incidence of PH in BPD ranges from 14 to 25%,[53] with a median prevalence in US centres of 14%.[54] PH in BPD is a predictor of increased mortality *(Figure 3)*[55,56] and also a significant risk factor for needing

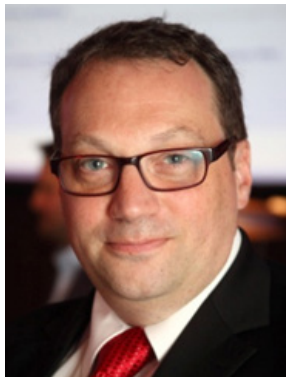
supplemental oxygen, tracheostomy, prolonged NICU stay and NICU readmission.[54] Pharmacological treatment of PH is focused on vasodilation with the aim of improving V/Q matching. The three main drug classes for the treatment of PH are prostacyclin analogues such as epoprostenol and treprostinil; endothelin receptor antagonists such as bosentan; and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil and tadalafil. There are as yet no evidence-based guidelines for the management of PH in BPD. However, a proposed standardised approach published in 2017 recommends that comprehensive echocardiography should be performed in patients with suspected moderate or severe BPD with signs and symptoms of PH, and repeated after optimisation of gas exchange and treatment of contributing co-morbidities, together with assessment of additional biomarkers including B-type natriuretic peptide (BNP) and N-terminal (NT)-pro BNP (NT-proBNP).[57] Cardiac catheterisation should be reserved for patients with severe PH and those who fail to improve.[57] In Professor Nelin's view, there is

a pressing need for biomarkers to identify infants with BPD at risk of developing PH, to enable early treatment and prevention of long-term sequelae.

Stem cells as a therapy

Regenerative therapy in the form of mesenchymal stem/stromal cells (MSC) is a promising avenue for repairing and restoring the "derailment" of development that occurs as a consequence of premature birth. Professor Boris Kramer from Maastricht University Medical Center in the Netherlands, presented an overview of the rationale for using stem cells in the NICU setting and summarised the available clinical data.

The effects of preterm birth and complications such as BPD on alveolar development are extremely complex, and will continue to affect outcomes into adulthood.[58] In Professor Kramer's view, waiting until 36 weeks' PMA, when a diagnosis of BPD can be made, is far too late to address the structural alterations in the blood vessels and alveolar structures of the developing lungs, and supplementing the necessary growth factors. "For an infant born extremely preterm, this can mean 10–12 weeks of missed treatment and opportunity for growth and differentiation," said Professor Kramer. Regenerative therapy based on stem cells has the potential to mobilise endogenous repair mechanisms, stimulate proliferation of affected cell populations and exert anti-apoptotic and anti-inflammatory effects,[59,60] and MSC therapy has been proposed as a treatment option for reducing inflammation and promoting vascular and alveolar growth and differentiation in preterm-born infants.[61] In a phase 1 study, nine preterm infants born at 25 weeks' GA received intratracheal transplantations of MSCs derived from human umbilical cord blood at two dose levels.[62] The results indicated that the treatment was safe and feasible, with no increased risk of adverse outcomes and favourable changes in the levels of inflammatory cytokines and growth factors.[62] After two years of follow-up, the safety data remained reassuring with no adverse respiratory, growth, and neurodevelopmental effects, and a suggestion of improved growth compared with controls.[63] These results paved the way for a randomised, controlled phase 2 study, which – although it confirmed the safety of MSC transplantation in this setting – failed to meet its primary objective of reducing the rate of death or severe/moderate BPD compared with controls, due to lack to statistical power.[64] Despite this setback, Professor Kramer remains confident that the basic principle of regenerative therapy for improving respiratory outcomes after preterm birth remains sound. Going forward, he advocates that the neonatology community should take a leaf out of the paediatric oncologists' book and adopt an approach similar to that used to develop an effective therapy for acute lymphatic leukaemia, with a single protocol used in all centres and subjected to regular revisions and improvements.[65]



Professor Boris Kramer, Maastricht University Medical Center, the Netherlands

For an infant born extremely pre-term, waiting until 36 weeks' PMA, when a diagnosis of BPD can be made, can mean 10–12 weeks of missed treatment and opportunity for growth and differentiation.

A major challenge is the impaired function of MSCs as they are transferred from the hypoxic conditions of their natural niche to standard cell cultures for expansion;[66] administering biologic therapies with the help of extracellular vesicles may offer a means of overcoming this challenge.[67] MSC-based therapies for the treatment of BPD remain a busy field of research, with several phase 1 and 2 studies currently in progress and expected to provide new data soon.

Ongoing Nordic studies and recent publications

As is customary, the 10th NNM included a round-up of ongoing and published research in the Nordic centres. The session was opened by Dr Anne Lee Solevåg from Oslo, who presented an overview of her research on how signs of myocardial injury can be used to diagnose and predict long-term adverse outcomes, including neurodevelopmental impairment, in asphyxiated infants. Dr Solevåg has developed a piglet asphyxia model for assessing biomarkers of myocardial perfusion and oxidative stress,[68,69] and has also conducted a feasibility study of a method for obtaining ECGs immediately after birth in asphyxiated infants, using a device developed for heart rate measurements.[70] Dr Solevåg speculated that comprehensive myocardial assessment may provide a novel approach to evaluating asphyxia and hypoxic ischemic encephalopathy (HIE) in near term and term infants, although this research is still in its early days and much remains to be done.

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Dr Charlotte Brix Andersson from Aalborg presented the results of a nationwide cohort study comparing the risk of complications associated with births early and late in the 42nd week of pregnancy, respectively.[71] The background for this study was uncertainty regarding the most appropriate timing of induction of labour in late-term pregnancies; a previous observational study on Danish data had shown an almost eight-fold increase in the cumulated risk of intrauterine foetal death from week 41+0 to 41+6.[72] The

Swedish Post-Term Induction Study (SWEPIS) showed that postponing birth induction until 42 weeks of gestation was associated with a higher risk of prenatal foetal death, prompting the WHO to change its recommendations accordingly. The nationwide cohort study presented by Dr Andersson included just under 135,000 births between 2009 and 2018, and found that pregnancies that continued beyond 41+4 weeks had a significant higher risk of neonatal death, hypothermia treatment, mechanical ventilation or nitric oxide treatment *(Figure 1)*.

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Next, Dr Krista Rantakari from Helsinki reported the findings of a database study in which infants born before 28 weeks' GA underwent neuroimaging at term and neurological examination at two years' corrected age, to determine the degree of correlation between oxygen levels during the first three days of life and later neuroanatomic changes and neurodevelopmental outcomes. A total of 73 infants were included in the study; the results showed that early hypoxia was associated with later white matter abnormalities, whereas early hyperoxia was associated with later cortical injury.[73] Both forms of abnormalities correlated with adverse neurodevelopmental outcomes at two years' corrected age, and the investigators concluded that the results emphasise the importance of maintaining strict saturation targets during the early postnatal period.

Dr Anne Lee Solevåg, Oslo University Hospital, Norway

Dr Charlotte Brix Andersson, Aalborg University Hospital, Denmark

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The initial results from the CORSAD randomised study were published in the summer of 2021 and were presented at NNM 2021 by Dr Snorri Donaldson who was the first author on the paper. The aim of CORSAD was to determine if a new respiratory support system with low imposed work of breathing (iWOB) and short binasal prongs for stabilisation of extremely preterm infants could decrease delivery room intubation or death compared with a standard T-piece system with face mask. A total of 250 infants born before 28 weeks' GA were included in the study and received CPAP for 10 to 30 minutes and PPV as needed. The primary endpoint analysis showed that 33.1% of the infants treated with the new system were intubated or died in the delivery room, compared with 45.1% of those in the T-piece group (adjusted OR 0.53; 95% CI 0.30, 0.94; P=0.03; *Figure 2*).[74] The CORSAD investigators concluded that the decrease in delivery room intubations may offer a window of opportunity for administering surfactant in a non- or minimally invasive way, avoiding mechanical ventilation.

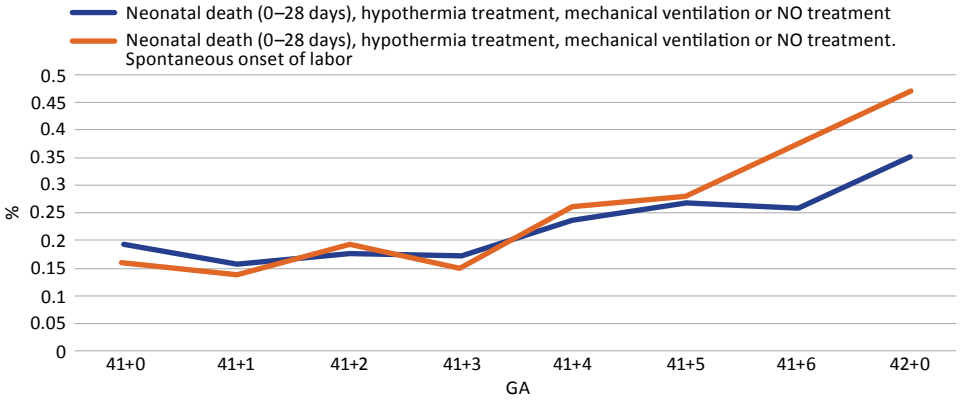

Figure 1. Composite neonatal outcome after births early and late in the 41st week of pregnancy, respectively. Reproduced with permission from the speaker.

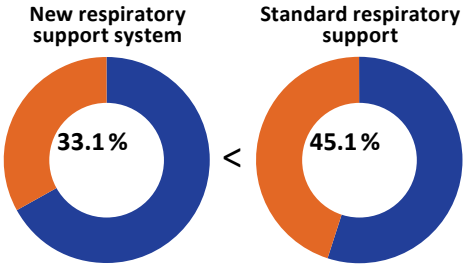

Figure 2. Incidence of intubation and death in the delivery room in the CORSAD study. Reproduced from Donaldson et al, 2021.[74]

New guidelines on neonatal resuscitation

In the concluding presentation of NNM 2021, Professor Charles Christoph Roehr summarised the recently published ILCOR recommendations for neonatal resuscitation,[75] and the ERC adaptation of the recommendations for Europe.[76] The ILCOR recommendations provide an assessment of all the available evidence in the area, and in doing so highlight all the major gaps in the evidence which makes them particularly interesting to clinical researchers. As the key messages in the recommendations, Professor Roehr highlighted evidence that delayed cord clamping improves survival and haematological and circulatory stability, especially in preterm-born infants; that keeping infants dry and warm together with stimulation is vital for breathing and oxygenation; and that peripheral oxygen saturation levels (SpO2) and heart rate should be frequently assessed. The intensity of the resuscitation effort should be guided by the need to achieve a target heart rate of over 100 bpm and SpO2 targets of 85% and 90% at five and ten minutes, respectively. Professor Roehr also stressed that many problems can be managed with simple airway and breathing support measures; and that chest compressions should only be used if the heart rate remains very slow despite adequate ventilation having been established.[75] ILCOR will continue to collaborate with regional bodies such as ERC on recommendations and evidence reviews to promote a high level of neonatal care and life support worldwide.

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