Nordic Neonatal Meeting News 2019

PRESENTATIONS FROM THE 9th NORDIC NEONATAL MEETING, 14–15 NOVEMBER 2019, HELSINKI, FINLAND

The 9th Nordic Neonatal Meeting took place in Helsinki, Finland on 14–15 November 2019 and was attended by neonatology specialists from all the Nordic countries. The presentations included updates on oxygen therapy within and beyond the delivery room, experiences with simulation and e-learning initiatives, evidence-based guidelines, and ongoing clinical trials. There was also a session that focused on development of the immune system in preterm infants and the importance of early microbial colonisation of the newborn gut.

Acknowledgements

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

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Oxygen during preterm stabilisation: some words of caution

Professor Máximo Vento,
University and Polytechnic Hospital La Fe,
Valencia, Spain

Failure to achieve adequate oxygen saturation during the first minutes of life can have grave consequences for preterm infants. Professor Máximo Vento from Valencia in Spain presented an overview of the management of oxygen levels during delivery room resuscitation and explained the correlation between low saturation, prolonged bradycardia and increased mortality and risk of IVH.

The fraction of inspired oxygen (FiO_2) used for delivery room resuscitation of preterm infants can affect short- and long-term morbidity and mortality. However, the optimal FiO_2 remains a subject of debate. The TORPIDO study showed significantly higher mortality after resuscitation with air (FiO_2= 21%) instead of 100% oxygen among babies born before 28 weeks' GA (RR 3.9; 95% CI 1.1, 13.3; p=0.03).[1] In contrast, no significant difference in mortality was observed among babies born later than 28 weeks' GA. A retrospective study reported by the Canadian Neonatal Network in 2015 indicated that switching to resuscitation with air instead of 100% oxygen increased the risk of severe neurological damage or death among infants born at or before 27 weeks' GA.[2] A meta-analysis of a total of eight studies and more than 500 infants born at or before 28 weeks' GA showed no difference in the overall risk of death or common morbidities including BDP, IVH or ROP after resuscitation with 30% or 60% oxygen.[3] Similarly, a Cochrane review found no difference in mortality or long-term neurodevelopmental disability among nearly 1,000 preterm infants resuscitated with FiO_2 below 40% or FiO_2=40%.[4] A recently published

Abbreviations

BDP	bronchopulmonary dysplasia	GA	gestational age	OR	odds ratio
CI	confidence interval	IVH	intraventricular haemorrhage	RDS	respiratory distress syndrome
CPAP	continuous positive airway pressure	LISA	less invasive surfactant administration	ROP	retinopathy of prematurity
CS	Caesarean section	NICU	neonatal intensive care unit	rRNA	ribosomal ribonucleic acid

systematic review of ten randomised controlled studies and four cohort studies comprising a total of nearly 5,000 infants born before 35 weeks' GA found no benefit or harm of FiO_2 at or below 50% compared with FiO_2 above 50% with respect to short- or long-term mortality or long-term neurodevelopmental impairment.[5] An abstract presented at the joint European Neonatal Societies (jENS) congress in September 2019 reported higher tidal volumes and inspiratory flow rates, shorter time on mask ventilation, and less hypoxaemia when infants born before 30 weeks' GA were stabilised with 100% oxygen compared with 30%, but found no significant difference in the need for intubation or the incidence of IVH or death.[6]

Another contentious issue is the achievement of targeted oxygen saturations in the delivery room for preterm infants. The European Resuscitation Council recommends a target oxygen saturation threshold of 85% at five minutes. An individual patient analysis of eight randomised controlled studies including a total of 768 infants born before 32 weeks' GA found that failure to achieve a saturation target of 80–85% was linked to a significantly higher risk of death or IVH.[7] In addition, infants who were resuscitated with <30% oxygen were less likely to achieve 80% saturation, and failure to achieve 80% saturation was associated with an increased risk of bradycardia, which in turn increased the risk of death.[7] Based on this rationale, the Bradyprem study analysed data from seven randomised controlled studies including a total of 535 infants born before 32 weeks' GA, and found that prolonged bradycardia (defined as a heart rate of less than 100 beats per minute persisting for two minutes or longer) was associated with significantly higher mortality and incidence of IVH.[8] A recent review has proposed targets for FiO_2 and saturation in the delivery room,[9] suggesting that resuscitation with air to a saturation target of 85% may be appropriate for preterm infants born before 29 weeks' GA, whereas resuscitation of infants born before 28 weeks' GA should be done with a higher FiO_2 of 30% (up to 40% in infants born before 26 weeks' GA) and aim for a saturation target of 80% *(Table)*.

Gestational age (weeks)	Initial FiO_2	Target SpO_2 at 5 min
>37 weeks	0.21	85–90%
33–36 weeks	0.21	85%
29–32 weeks	0.21–0.30	80–85%
<28 weeks	0.3	80%
<26 weeks	**0.3–0.4**	**80%**

Table. Suggestions for oxygen supply in the delivery room.[9]

Oxygen beyond the delivery room

Professor Benjamin J Stenson, Royal Infirmary of Edinburgh, United Kingdom

Oxygen therapy is an essential part of caring for preterm infants and maximising survival; however, exposure to excessive oxygen can lead to significant morbidity and saturation levels therefore have to be carefully balanced. In his presentation, Professor Benjamin Stenson from Edinburgh discussed how achieving oxygen targets will influence outcomes, and highlighted the need for high-quality studies to determine the optimal level of oxygen saturation.

There has been a considerable change in practice with respect to oxygen use in neonatal units in recent decades. Continuous blood gas analysers and pulse oximetry have enabled routine monitoring of transcutaneous tissue oxygen tension ($TcPO_2$) and peripheral capillary oxygen saturation (SpO_2); however, for a long time the saturation targets for this monitoring were based on physiological reasoning and observational findings, rather than prospective randomised studies. An attempt at relating saturation targets to outcomes was published in 2001, when a group of British investigators reviewed case notes of 295 infants born before 28 weeks' GA and showed that a higher saturation target of 94–98% was associated with a four-fold increase in the risk of ROP as well as prolonged time on ventilation and oxygen compared with a lower target of 80–90%, with no significant differences in survival or signs of cerebral palsy at one year.[10] These findings, along with other studies, encouraged prospective studies and gave rise to the NeOProM studies. This is a collaboration of five independent studies where the study design and protocol were aligned to allow meta-analysis of the final results.[11] In NeOProM, infants born before 28 weeks' GA were randomised to oxygen saturation targets that were either low (85–89%) or high (91–95%) within the first 24 hours of life, and treatment continued for up to 36 weeks. The meta-analysis included 4,965 infants with a median GA of 26 weeks, and showed statistically significantly higher mortality among infants randomised to the lower saturation target (RR 1.17; 95% CI 1.04, 1.31; p=0.01).[12] The absolute difference in mortality of 2.8% accounts for approximately one in every seven deaths in the lower saturation target arm. No significant difference was seen in the primary outcome which was a composite of death or major disability (blindness, deafness, cerebral palsy or cognitive disability). Treatment for ROP was more prevalent in the higher saturation target arm, but there was no statistically significant difference in the rate of blindness. The NeOProM protocol also recorded the rate of NEC, defined as either requiring surgery or causing death – this outcome was significantly more common in the low saturation target arm.[12]

While the NeOProM results point to a significant survival advantage of targeting higher oxygen saturation for preterm infants, the optimal target level has yet to be defined. Post hoc analyses of results from individual NeOProM studies highlight that the achieved saturation levels in the higher and lower target arm, respectively, were considerably closer than intended, suggesting that the differences in outcomes noted in the study were the result of relatively small differences in exposure. This was especially evident when considering survivors separately: in the BOOST-II UK study babies who survived were found to have spent much of their time at a saturation level of 94–95% irrespective of randomisation, whereas the babies who died in the lower saturation target arm had peaked at a saturation of 90–91%.[13] Matching the infants who died to survivors in the low and high target arm, respectively, indicates that the main predictor of survival is not the time spent at extremely low saturation levels, but rather to the time spent in the 84–92% range. Similarly, survival data from the SUPPORT study showed significantly higher mortality among infants who failed to achieve a median oxygen saturation target of >92% irrespective of randomisation.[14] Professor Stenson stressed that while the best evidence currently supports aiming for the higher targets in the NeOProM studies, further research is needed to explore how outcomes are affected by achieved saturation levels. Any new intervention that alters SpO_2 distribution is likely to influence clinical outcomes.

"While the NeOProM results point to a significant survival advantage of targeting higher oxygen saturation for preterm infants, the optimal target level has yet to be defined."

Hypoxemic episodes in preterm infants – are automated adjustments helpful?

Professor Helmut Hummler,
Sidra Medicine and Weill Cornell Medicine – Qatar, Doha, Qatar

Controlling oxygen saturation levels in arterial blood is vitally important in preterm infants, since both hypoxaemia and hyperoxaemia can have severe clinical consequences. The process of monitoring and adjusting oxygen administration in neonatal units is becoming increasingly automated. Professor Helmut Hummler from the Sidra Medicine Hospital in Qatar reviewed some of the currently available solutions for closed-loop automated control.

Investigators at the University of Miami have developed a system for automated oxygen control that is marketed under the name CLiO$_2$™, which is short for Closed Loop Controller of Inspired Oxygen. In a pilot study of this device in 14 infants with a median GA of 25 weeks, the time spent within a target range of 88–96% was significantly longer with the closed loop system than with routine manual adjustment.[15] In addition, the closed loop system was also associated with numerically less time spent at saturations above 96% and below 85%, although these observations did not reach statistical significance. Further randomised cross-over studies showed a similar difference in favour of the CLiO$_2$ device over routine manual monitoring with respect to the time spent within the target range and in hyperoxaemia; however, a small but significant increase in the time spent at saturation levels below 88% was noted with the closed loop system.[16, 17] Although no significant difference was found in the time spent at saturation levels below 70%, regulatory concerns that the risk of hypoxaemia with automated monitoring may have led to a delay in the CLiO$_2$ becoming available for clinical use in the United States. Further randomised studies in preterm infants with frequent desaturations and in larger patient populations have since confirmed that CLiO$_2$ does not increase exposure to desaturations.[18, 19]

Another device that has been shown to improve oxygen control over routine manual adjustment is the Leoni® device which was developed in collaboration with experts from the University of Tübingen in Germany. A randomised cross-over study in 12 infants with a median GA of 26 weeks showed that the closed loop system achieved significantly longer time spent within a saturation target range of 87–96% compared with routine manual control, comparable to that achieved with having an investigator permanently at the bedside making adjustments.[20] A randomised, cross-over multicentre study in 34 infants confirmed that the Leoni device significantly prolonged the time spent within a set target range, and also significantly reduced the number of manual oxygen adjustments compared with routine manual control.[21]

More recently, Professor Hummler and his team have developed a new device for closed loop oxygen control called Sophie®. A randomised crossover study in 12 infants with a median GA of 25 weeks showed that the closed loop system significantly prolonged the time spent within a target saturation range of 88–96% compared with routine manual control, with a dramatic reduction in the number of manual adjustments required, from 7.5 adjustments per hour on routine manual control to 0.5 adjustments per hour on Sophie[22] which would represent a significant decrease in caregiver workload in clinical practice. The Sophie system was especially effective for limiting the number of longer desaturations.

"In my opinion, there is nothing to replace a good neonatal nurse."

While currently available systems for clinical care have been shown to prolong the time within target ranges and reduce the rate of extreme hypo- and hyperoxaemia, Professor Hummler advised caution. Randomised controlled studies of long-term exposure are needed to document the long-term outcomes with automated oxygen control, and the technical limitations of automated systems need to better understood, including the risk of erroneous adjustments due to low perfusion. "In my opinion" Professor Hummler stated by way of conclusion, "there is nothing to replace a good neonatal nurse."

The use of NAVA ventilation in neonates

Dr Hanna Soukka,
Turku University Hospital, Finland

Neurally adjusted ventilatory assist (NAVA) is a mode of mechanical ventilation that triggers, cycles and delivers assist in response to the electrical activity of the diaphragm (EAdi), a signal arising from the neural activation of the diaphragm during spontaneous breathing. It can be used for premature infants, including very immature infants provided there is enough respiratory drive, and has been shown to reduce peak pressure and improve the interaction between the infant and the ventilator. Dr Hanna Soukka from Turku University Hospital presented an overview of NAVA and described the experience with NAVA ventilation in the Turku NICU.

To date NAVA has been documented in one randomised study in 60 infants with a mean GA of 31 weeks.[23] The duration of invasive ventilation, which was the primary endpoint in this study, was numerically longer in the NAVA arm compared with the arm receiving conventional ventilation, but this difference was not statistically significant. Secondary outcomes included significantly lower peak inspiratory pressures in the NAVA arm; no significant differences were noted in the rate of BPD, pneumothorax or IVH.[23] In addition, several randomised and non-randomised crossover studies and retrospective cohorts have also shown that NAVA is associated with lower peak inspiratory pressures[24–31] and that NAVA improves patient-ventilator synchrony.[24, 25, 29, 32] NAVA was introduced in the NICU at Turku University Hospital in 2009 and is used as the primary mode of ventilation for all neonates who are expected to be ventilated for longer than 24 hours. The main advantage of NAVA is that it is a gentle form of ventilation with continuous monitoring of the respiratory drive, which allows for optimisation of positive end-expiratory pressure and analgesics. In addition, parents and neonatal nurses agree that it provides more comfort for the infant compared with conventional ventilation.

Immune system development and infectious disease susceptibility in preterm and term children

Dr Petter Brodin,
Karolinska Institute, Stockholm, Sweden

The human immune system is largely shaped by exposure to environmental factors throughout life. Studying the immune system in newborn infants can provide insight into how early disturbances can affect health outcomes later in life. Dr Petter Brodin, senior researcher in immunology at Karolinska Institute in Stockholm, delivered a keynote lecture on how the immune system develops and adapts in the very period of life in preterm and full-term infants.

The first critical event in the development of the human immune system is the birth, when the infant emerges from a protected environment *in utero* to face an onslaught of microbial colonisation during and after the delivery. Data from a birth cohort set up by Dr Brodin and his team in Stockholm, in which 100 preterm and full-term infants and their parents provided blood samples at birth (cord blood) and at one, four and twelve weeks after birth, shows that compared with full-term infants, preterm infants are born in the middle of a cytokine storm, with dramatically elevated levels of highly pro-inflammatory factors such as IL-8 and CXCL11 measured in cord blood.[33] However, these cord blood measurements were in no way representative of immune cell frequencies or plasma protein levels only one week later, indicating that the immune system immediately begins adapting and responding to its environment after birth in a way that cannot be predicted from cord blood. In this context, cord blood is simply an outlier.

While the initial postnatal development immune system is characterised by a high degree of variation, this appears to change rather drastically at around 100 days of life. At around this time, the relative abundance of immune cells and plasma proteins appears to become much more stable. This is especially interesting in light of epidemiological studies that have identified the first 100 days of life as a critical period for developing conditions such as asthma, allergy and inflammatory bowel disease.[34–43] In their studies in preterm and term infants, Dr Brodin and his team have observed distinct patterns in how the immune system develops in the first year of life, from initial expansion of classic monocytes and activated memory T-cells to waves of B-cells and effector T-cells. A key driver of these waves is believed to be the gut microbiome – in the first 100 days of life, the proportion of cells of gut origin in the blood increases from around 30% in cord blood to nearly 70%, before gradually returning to the levels seen in adult individuals. To establish the infant gut microbiome, the immune system must be attenuated for a period so as to not attack the colonising species; this attenuation of the immune system has been linked to elevated levels of epidermal growth factor (EGF) in breast milk. In mice, this period of establishing the gut microbiome and deciding which microbes to keep comes to an end at weaning;[44] in humans, it is associated not with weaning but with a distinct reduction in breastmilk EGF levels which occurs just before 100 days of life. Around this time there is also a massive expansion of Bifidobacterium species in the infant gut, irrespective of the mode of delivery. Bifidobacterium are known to produce short-chain fatty acids that have a favourable effect on the developing immune system. Dr Brodin's research has shown that high abundance of Bifidobacterium species in the gut is associated with reduced inflammatory markers (unpublished data).

> *"Preterm infants are born in the middle of a cytokine storm."*

Transmission of maternal antibodies across the placenta is important for protecting the newborn infant from infections in early life. Using an innovative method for detecting antiviral antibodies in human serum,[45] Dr Brodin and his team found no differences between preterm and term infants with respect to the repertoire of antibodies or the ability to neutralise respiratory syncytial (RS) virus until the age of twelve weeks.[46] One explanation for this may be that although preterm infants have lower amounts of circulating antibodies at birth, antibodies transferred earlier in the pregnancy may have higher functional capacity.

Long-term follow-up after necrotising enterocolitis and bowel perforation – a PhD project

Dr Nina Hapnes,
Stavanger University Hospital, Norway

Necrotising enterocolitis (NEC) is a severe complication that affects 6–9% of extremely preterm infants in Scandinavia and is associated with a mortality rate of up to 40%.[47, 48] Some infants also develop spontaneous intestinal perforation (SIP), without the bowel inflammation and necrosis that is characteristic of NEC.[49] Dr Nina Hapnes from Stavanger is about to begin a PhD project which aims to identify risk factors for NEC and SIP, assess the disease burden, and study the long-term impact of surgery for NEC and/or SIP with the ultimate goal of identifying areas where the follow-up of these infants can be optimised. The PhD project includes three substudies: the first two will utilise data from the Swedish Neonatal Quality Register and the Norwegian Neonatal Network to provide updated and detailed knowledge on risk factors, epidemiology, management and survival to discharge among infants with NEC or SIP in Norway and Sweden. The third substudy will be a clinical observational case-control study which will collect long-term follow-up data on health-related quality of life (HRQoL; primary endpoint), growth, development, biochemical nutritional status and persistent gastrointestinal symptoms at school age after surgical treatment of NEC or SIP during the neonatal period. This study will include all cases in Norway over a period of six years, with two controls included per case. This study will be the first to collect data on biochemical nutritional status alongside HRQoL, growth and development. The third substudy has received ethical approval and is expected to begin including participants in early 2020. Dr Hapnes is hoping that this project may stimulate further collaboration across national borders and medical registries in the Nordic countries.

Perinatal determinants of microbiota development

In the first days and weeks after birth, the gut microbiome in preterm infants is distinctly different from that in babies born at term, which is believed to have adverse consequences for their health in the longer term. Dr Samuli Rautava from Turku University Hospital discussed the factors that influence early colonisation and the development of the gut microbiome in preterm infants, and outlined the link with antibiotic resistance.

The chaotic initial colonisation of the gut in preterm infants may be due to the fact that the immune system is immature and the intestinal mucosa not ready to be colonised. Another risk factor is the environment into which preterm infants are born, with CS delivery, exposure to antibiotics, often delayed breast feeding and impaired skin-to-skin contact.[50] Gut dysbiosis in preterm infants has been shown to affect weight gain[51] and has been connected with very severe complications including NEC[52] and late-onset sepsis.[53] Study results from Dr Rautava's unit indicate that prematurity itself may be an independent risk factor for gut dysbiosis, in addition to factors such as antibiotic exposure, mode of delivery and breastfeeding.[54] An experimental study in which meconium from very preterm (VPT), preterm (PT) and full-term (FT) infants was used for microbiota transfers to germ-free mice found that the meconium from VPT infants induced a phenotype of growth failure, decreased levels of metabolic markers including insulin and leptin, and immune activation with elevated levels of pro-inflammatory cytokines.

Dr Samuli Rautava, Turku University Hospital, Finland

The maternal gut and breastmilk microbiome has been shown to affect the abundance of antibiotic resistance genes in infants born at term irrespective of exposure to antibiotics.[55] In a study in preterm infants, antibiotics alone had little or no effect on antibiotic resistance genes, whereas inclusion of formula in the diet caused the microbiome composition to shift towards higher antibiotic resistance load and increased abundance of Enterobacteriaceae species, suggesting a higher risk of opportunistic pathogens and infections in infants fed with formula rather than breastmilk.[56]

> *"When used for microbiota transfers to germ-free mice, the meconium from very preterm infants induced a phenotype of growth failure, decreased levels of metabolic markers, and immune activation."*

Maternal faecal transplantation to infants born by Caesarean section – safety and feasibility

The link between early microbial colonisation of the newborn gut and health later in life is well known, and considered a contributing factor in the development of conditions such as asthma and inflammatory bowel disease. Infants born by CS have been shown to have less heterogeneity in their gut microbiome, with lower abundance of, for example, Bifidobacterium and Bacteroides species. With the global rise in the number of CS births there is a need for interventions to correct imbalances in the gut microbiome as early as possible. Dr Otto Helve from Helsinki reported on a study that investigated the safety and feasibility of oral administration of faecal microbiota transplantation (FMT) from mothers to infants born by CS. Two weeks prior to delivery, the mothers provided faecal samples which were suspended in saline and frozen after rigorous safety testing for infections. Within two hours of delivery, the FMT was mixed with breast milk or formula and administered as the first feed. The FMT was well tolerated by all seven infants, with no clinically significant increases in inflammatory markers. One infant who received 7mg of FMT instead of 3.5mg had a transient increase in CRP to 67mg/l, with no clinical symptoms or need for antimicrobial treatment. Faecal samples from the infants were analysed using 16S rRNA sequencing and the results compared with non-treated infants born vaginally or by CS. The samples from infants born by CS and treated with maternal FMT closely resembled those from infants born vaginally, with significantly greater abundance of Bifidobacterium and Bacteroides species compared with infants born by CS. The investigators concluded that maternal FMT is safe and feasible for restoring the gut microbiome in infants born by CS. A randomised double-blind study is currently in progress to document the long-term effects.

Dr Otto Helve, Children's Hospital, Helsinki University Hospital and the University of Helsinki, Finland

Machine learning in neonatology

Artificial intelligence describes processes whereby machines – typically computers – can simulate human intelligence, by using machine-learning (ML) algorithms that mimic cognitive functions to solve problems and make predictions from new data. Dr Markus Leskinen from Helsinki described how ML is being implemented at the Children's Hospital NICU in Helsinki and outlined some of the challenges for the future.

Artificial intelligence is already in widespread everyday use by providers such as Netflix and Amazon, for making recommendations based on ML algorithms that monitor users' searches and purchases. Unlike rule-based systems, ML algorithms learn without any premade rules and can be taught to predict outcomes without explicit programming, based on large amounts of data and known results.

A NICU is a data-intensive environment where large amounts of data are

Dr Markus Leskinen, Children's Hospital, Helsinki, Finland

continuously collected from patient monitors, medical devices, laboratory results and numerous other measurements and endpoints, making it highly suitable for ML. Dr Leskinen and his team have completed a pilot project in the NICU setting in which ML was used to predict late-onset sepsis in very low birthweight (VLBW) infants. In this project, data was collected from electronic health records in NICU units in the Helsinki region on more than 2,000 VLBW infants born between 1999 and 2013, 173 of whom with late onset sepsis confirmed by positive blood cultures and clinical diagnosis, and 106 with suspected sepsis but with negative blood cultures. The algorithm collected data to identify patterns that accurately predicted sepsis 24 hours prior to the positive blood culture. By subjecting the collected data to an exhaustive Chi-squared Automatic Interaction Detector (CHAID) decision tree model, a prediction model could be developed that could identify blood positive sepsis with 82% sensitivity and 96% specificity, with a positive predictive value of 0.88 and a negative predictive value of 0.94 *(Figure)*.

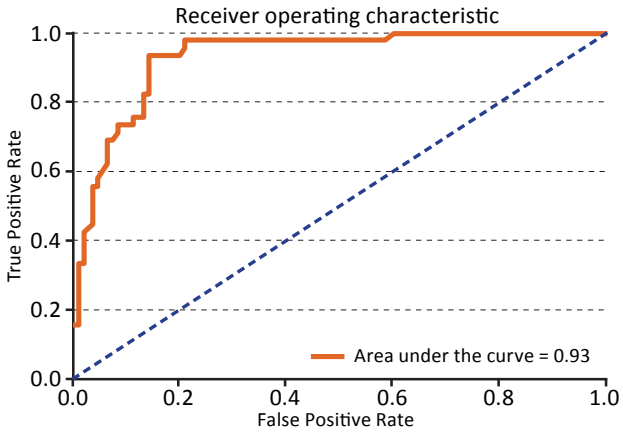


Figure. ML prediction model of sepsis 24 hours prior to positive blood culture.

The main advantage with ML over rule-based expert systems is its ability to detect patterns in complex datasets, and lack of time- or user-dependent variability. Limitations include its lack of transparency and tendency to generate very detailed predictions regardless of the quality of the data input. As ML becomes more common, interface overload may become a barrier to its use. More research is needed to determine the benefit of AI in a clinical setting.

European guidelines for the management of RDS 2019

The first European guidelines on the management of RDS were published in 2007 in the Journal of Perinatal Medicine.[57] Since then, the guidelines have been updated every three years with the overall aim of examining the evidence and making consensus recommendations. In a keynote lecture at this year's NNM, Dr David Sweet from Belfast introduced the 2019 version of the guidelines[58] and highlighted some key changes from 2016.

The scope of the guidelines is comprehensive and covers all aspects of lung protection and respiratory support. The strength of the evidence is graded from A (representing high-quality randomised controlled studies and unbiased observational studies) to D (representing expert option in the absence of published data), and the strength of the recommendations is graded as 1 ("we recommend") or 2 ("we suggest").

In the prenatal period, it is strongly recommended (C1) that women expected to have a preterm birth should be transferred to a high-throughput perinatal centre and be offered a single course of antenatal corticosteroids (A1). A second course of steroids can be considered a couple of weeks later if the birth is expected before 32 weeks' GA (A2). The 2019 update also includes a new recommendation

Dr David Sweet, Royal Maternity Hospital, Belfast, United Kingdom

that antenatal magnesium sulphate should be administered as a neuroprotective agent (A2).

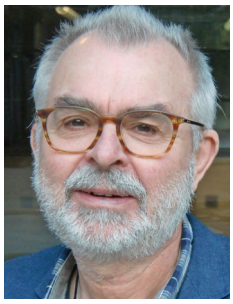
Recommendations for stabilisation in the delivery room include delaying cord clamping for at least 60 seconds (A1); administering oxygen therapy with an initial FiO_2 of 30% for infants born before 28 weeks' GA, and 21–30% for infants born at between 28 and 31 weeks as guided by pulse oximetry (B2); avoiding sustained inflation (B1) and reserving intubation for infants who fail to respond to positive pressure ventilation via face mask (A1).

For infants who require surfactant therapy, the surfactant should be of natural origin (A1) and poractant alfa at an initial dose of 200mg/kg is superior to poractant alfa at half this dose or beractant (A1). Surfactant should be given early in the disease course (B2). LISA is the preferred mode of administration of surfactant for infants on CPAP, provided that it is in the hands of experienced clinicians (B2).

Beyond the delivery room, CPAP should be started in all infants at risk of developing RDS who do not require intubation (A1), at a starting pressure of approximately 6–9cm H_2O and using short binasal prongs or a face mask (A2). A strong recommendation is that CPAP with early surfactant should be considered the optimal management for infants with RDS (A1). After stabilisation, mechanical ventilation should be used when other means of respiratory support have failed (A1). If conventional mechanical ventilation is used, targeted tidal volume ventilation should be used (A1). Caffeine should be used to facilitate weaning from mechanical ventilation (A1). In infants who remain on mechanical ventilation after one to two weeks, a short course of dexamethasone may be considered to facilitate extubation (A2). Inhaled budesonide can be considered for infants at high risk of BDP (A2).

Simulation in neonatology

Simulations are an essential part of neonatal care. Dr Anders Dahlström, consultant neonatologist at Stockholm South Hospital (Södersjukhuset) pioneered the introduction of simulations in obstetric wards in the late 1990s and is now regarded as the "father of simulation" in Sweden. The concept created by Dr Dahlström and co-workers is called Concept for Patient Simulation (CEPS) and utilises adult learning theory and video-based debriefing to deliver training under realistic conditions, focusing on the team and each team member's responsibility in a safe learning environment. Simulation can be used for practicing both technical skills such as intubation and umbilical catheter placement, and non-technical skills including communication and leadership.



Dr Anders Dahlström, Stockholm South Hospital, Sweden

A report by the US Joint Commission on Accreditation of Healthcare Organizations published in 2004 found that lack of communication and failure to work as a team were among the most common root causes or errors leading to perinatal death or permanent disability, and the Commission recommended that teams should complete simulator training to improve teamwork, leadership and communication.[59] Dr Dahlström stressed the importance of having training and simulations in the actual teams that are expected to work together in the clinic, to ensure that the simulated scenario is relevant for the entire team. By using a low-fidelity manikin covered in blood and mucus and simulating abnormal heart rates and respiration, the simulation can be performed under very realistic conditions (high-fidelity scenario) that closely mimics the stress of performing a delivery room resuscitation. In the video debriefing each team member gets to see everything that has happened during the simulation, allowing for reflection on their own behaviour and possibly change. Other challenging situations that can be simulated include neonatal ambulance transports, and communicating with parents in the NICU and bringing bad news.

Dr Hanna Soukka, Turku University Hospital, Finland

Dr Hanna Soukka reported the results from the Nordic simulation survey which was carried out among neonatologists, paediatricians and residents in delivery hospitals in Denmark, Finland, Norway and Sweden. Around half of the hospitals approached responded to the survey; of those who responded nearly all perform simulations in the NICU or delivery room or in separate simulation facilities. Simulations tend to last from around one hour up to a whole day, and involve multiprofessional teams. The number of performed simulations corresponded well with the number of scheduled simulations – interestingly, when asked about the number of neonatal simulations in the hospital, residents in Sweden and Finland stated that it was enough whereas residents in Norway and Denmark thought it was too low *(Figure)*. The main areas covered in simulations were leadership and communication, together with technical skills such as mask ventilation and chest compressions. Only one in three hospitals reported doing any form of evaluation of the effectiveness of simulation training, mainly in the form of questionnaires and verbal feedback.

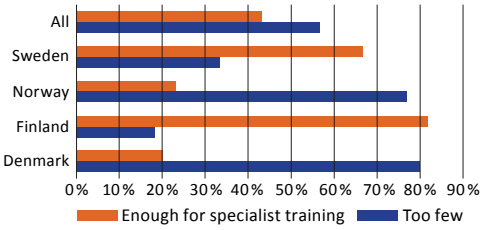


Figure. Are there enough neonatal simulations in your hospital, or too few?

e-learning and e-follow-up for neonatologists

Digital applications for training and follow-up are increasingly integrated into healthcare to help target resources and improve the quality of care. A session at NNM 2019 showcased e-learning and e-follow-up initiatives that are being implemented in Nordic neonatal units.

Dr Riikka Korja from the University of Turku in Finland presented an overview of a project for digital follow-up of preterm infants and their families, which has been developed by Turku University Hospital in collaboration with health data science company Kaiku Health. In digital follow-up, assessments are performed at eight time points from the day of birth until the age of two years to evaluate the infant's health, growth and development and the family's well-being, using a combination of standardised validated instruments and self-developed questions. As a crucial part of the project, parents receive evidence-based information and support packs at each assessment point. A validation study is currently in progress in the Turku University Hospital NICU which will evaluate the extent to which the Kaiku Health tool can detect problems early to allow targeted support, and reduce the number of paediatric outpatient clinic visits and contacts.

Dr Rikke Kaae from Aarhus University Hospital in Denmark presented a study from her PhD thesis which evaluated the effect of using e-learning for improving neonatologists' skills in ultrasonography (US)-based examination of umbilical catheter placement in neonates. US has previously been shown to be more accurate for detecting umbilical catheter placement versus x-ray. The e-learning tool consisted of a 1.5-hour web-based programme in which all 48 neonatologists at Denmark's four university-based NICUs participated. Multiple-choice assessments before and after the e-learning programme indicated that the baseline knowledge of US for umbilical catheter placement significantly correlated with the participant's self-reported US experience prior to e-learning. However, this variation in knowledge disappeared after completion of the e-learning programme, and the investigators concluded that the use of a short e-learning programme was a feasible approach for providing all neonatologists in Denmark with a common knowledge base on how to perform US for umbilical catheter placement.

Dr Riikka Korja, University of Turku, Finland, Dr Rikke Kaae, Aarhus University Hospital, Denmark, Dr Sari Ahlqvist-Björkroth, University of Turku, Finland

In the final talk Dr Sari Ahlqvist-Björkroth from the University of Turku described the e-learning module within the Close Collaboration with Parents (CC) training programme, which has been developed at Turku University Hospital to improve the skills within the NICU healthcare team with respect to interaction and communication with parents of preterm infants. The CC programme consists of four phases with defined learning goals. Each phase includes both theoretical learning and practical exercises; this structure is reflected in the e-learning module which can be accessed and completed independently by the members of the NICU team and is intended to supplement the practical, mentor-led bedside exercises. The e-learning module is currently available for units that have participated in the training programme – once the acceptability and feasibility of the module have been studied, it may be made available as an independent e-learning course for NICU professionals.

Ongoing Nordic studies

A fixture on the NNM programme is a round-up of planned, ongoing and completed clinical studies in Nordic centres. The first study in this session was presented by Dr Kirsti Haaland from Oslo University Hospital in Norway. This study forms part of the Twilight of Antibiotics project, a collaboration between hospitals in Norway, Denmark and India which aims to understand the development of the respiratory microbiome in preterm infants and the risks posed by antibiotic resistance genes. Inclusion in the study is ongoing; to date, 15 out of a planned 360 preterm infants (28–32 weeks' GA) have been included. Nasopharyngaeal aspirates and faecal samples will be analysed using sequence-based and functional metagenomics – a key challenge will be to deplete human DNA in the samples and extract sufficient microbial DNA for the analyses.

Dr Kirsti Haaland, Oslo University Hospital, Norway, Professor Baldvin Jónsson, Karolinska University Hospital, Stockholm, Sweden,

Professor Baldvin Jónsson from Karolinska University Hospital in Stockholm provided an update from the CORSAD study, an ongoing randomised multicentre study to document a new system for respiratory support for initial stabilisation of preterm infants. In this study the new system, which imposes a low work of breathing and is administered using nasal prongs, will be compared to a standard T-piece system which uses a face mask. A total of 250 infants born before 28 weeks' GA will be randomised to the new system or standard support at seven centres in Sweden, Norway, Iceland, Lithuania and Poland. The primary outcome is a composite of intubation in the delivery room or death. To date, a total of 198 infants have been randomised. The study is expected to finish in the early part of 2020.

Dr Lise Aunsholt from Rigshospitalet in Copenhagen presented a research project on the safety and benefits of bovine colostrum in preterm infants. The rationale for this project was that bovine colostrum contains high concentrations of micro-and macronutrients that promote growth and intestinal maturation, and could potentially reduce the need for parenteral nutrition in preterm infants. In the first study, bovine colostrum was well

tolerated by infants after intestinal resection, with no signs of milk allergy.[60] Two randomised studies, PreColos and FortiColos, are currently in progress in centres in Denmark and China and will investigate the feasibility of administering bovine colostrum as first feed[61, 62] and fortifier,[63] respectively, in preterm infants.

The session on ongoing studies concluded with a presentation by Dr Christian Heiring from Rigshospitalet of a novel test for predicting RDS and guiding surfactant treatment in preterm infants. The novel test involves determining the lecithin/sphingomyelin ratio (L/S) in gastric aspirates from premature infants by measuring surface-active lung phospholipid dipalmitoylphosphatidylcholine and sphingomyelin by Fourier transform mid-infrared spectroscopy (FTIR). An initial observation study in 136 preterm infants with a median GA of 29.1 weeks utilised frozen samples and found that an L/S cut-off ratio of 2.2 could predict RDS with 92% sensitivity and 73% specificity.[64] A second study utilised fresh samples, on the basis that this would be more feasible for point-of-care testing; this study included 72 preterm infants and resulted in an L/S cut-off ratio of 3.05 which predicted RDS with 91% sensitivity and 79% specificity.[65] A further observational study is currently in progress in China, and a randomised controlled study is planned to assess the safety and benefit of L/S-guided early surfactant treatment.

Dr Lise Aunsholt and Dr Christian Heiring, Rigshospitalet, Copenhagen, Denmark

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