Neonatology

Extended Abstracts

Neonatology 2020;117:389–409
DOI: 10.1159/000505853

Published online: October 6, 2020

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Cardiopulmonary Transition of Preterm Infants at Birth: Optimal Strategies for Support and Stabilization

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During the transition to life after birth, lung aeration is pivotal for the changes in respiratory and cardiovascular function that are required for survival.[1] However, our understanding of factors controlling breathing in preterm infants at birth is limited and so our ability to optimize non-invasive strategies to support the transition from fetal to newborn life is limited. Most preterm infants fail to aerate their immature lungs and need respiratory support [2] and cord clamping then compromises cardiovascular function. This can have severe consequences for the infant as even short periods of inappropriate support can induce lung and brain injury.[3]

To minimize injury, non-invasive ventilation strategies (NIV; positive pressure support of breathing and/or ventilation via face-mask) are now universally adopted as the first choice for respiratory support at birth.[2, 4] However, little is known about how they interact and integrate with the infant's changing physiology. While we assumed that the applied pressure is transmitted into the trachea, this assumption now appears to be incorrect.[5, 6] In newborns with a unstable breathing pattern at birth, the larynx is adducted and only briefly opens during a breath. [7] There is a need for strategies that stimulate and support breathing and avoid factors that impede or inhibit breathing to optimize the success of NIV at birth.

Based on the rationale that a preterm infant can benefit from a placental transfusion, cord clamping is now delayed for 30-60 seconds if the clinical condition of the infant allows it.[8] However, this time-based cord clamping approach does not take into account whether the infant has aerated their immature lungs. Cord clamping before the infant commenced air-breathing greatly reduces the infant's cardiac output at birth, which increases the risk for hypoxic ischemic injury.[9, 10] Also, the sudden loss and then rapid recovery of cardiac output (following lung aeration) increases the risk of cerebral vascular injury.[10] Waiting with cord clamping until the infant is stable and breathing (physiological based cord clamping) has been shown to be safe and feasible. [11] Less bradycardia and hypoxia was observed, supporting the more stable hemodynamic transition described in the animal studies. [11] Currently, large trials in preterm infants are underway to investigate whether physiological based cord clamping improves important clinical outcome when compared to time-based cord clamping.

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Management of the Severely Compromised Term Infant

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Attending severely compromised newborn babies who are in need of intervention at birth can be a highly challenging task. Incomplete adjustment at birth, resulting in significant cardiorespiratory compromise may have many causes which are not always imminently apparent. International newborn resuscitation guidelines advise on certain aspects of resuscitation, particularly advising a focus on airway-breathing-circulation algorithms [1–3]. However, different to the preterm population where measures of support of their fetal-to-neonatal transition have been in the spotlight of much translational research, far less certainty from higher grade evidence is currently available to guide term born resuscitation.

In this paper, a review of the evidence-base of common interventions applied during term-born resuscitation is given. We suggest that an in-depth understanding the normal physiology of fetal-to-neonatal transition is mandatory as this will help with understanding and tackling the pathophysiology of common reasons for term-born infants' compromise [4]. Such knowledge also will assist with planning resuscitation of compromised term newborn infants. Whilst immediate provision of advanced life support is necessary, it is important to act on as much evidence as possible to be effective and at the same time limit the potential for iatrogenic, long-term harm. Below, the latest evidence synthesis for specific resuscitative measures will be given and areas of urgently needed research be highlighted.

For resuscitation of infants born at or near term, newly emerging evidence points towards benefits of initiating resuscitation whilst delaying umbilical cord clamping [4, 6]: As shown by in a large scale clinical trial by Andersson et al., including over 1500 late preterm and term born infants, resuscitation with an intact umbilical cord improved SpO_2 and resulted in higher Apgar scores, in absence of negative infant or maternal consequences [6]. This information adds significantly to the already well-established benefits of delaying cord clamping in non-compromised infants [7]. Further certainty was gained over the past five years regarding managing the infant born through meconium-stained amniotic fluid. Comprehensive review of the most recent data from randomised clinical trials by the ILCOR (international liaison committee on resuscitation) neonatal task force has led to a suggestion of change in practice, advising for immediate commencement of respiratory support and against routine immediate direct laryngoscopy after delivery [9]. For commencing respiratory support, high certainty exists regarding the advised initial oxygen concentration for term born infant, compared to lesser certainty for preterm infants. For the infant born at or above 35 weeks gestation, sufficient evidence exists to strongly advise for a starting fraction of inspired oxygenation (FiO_2) of 0.21 [1, 5]. When applying additional oxygen during stabilisation, it is advised to monitor oxygenation by pulse oximetry and taper the fraction of inspired oxygen against published nomograms [1].

Maintaining normothermia during initial resuscitation is vital in order to minimise morbidity and mortality. Thus, therapeutic hypothermia should not be initiated during the immediate resuscitation as it remains a targeted treatment for infants with signs of encephalopathy [9].

Whilst it is acknowledged that the long-term outcomes of even severely depressed newborns with Apgar-scores of zero is not necessarily catastrophic, it seems prudent to have a local resuscitation protocol which includes a sensible approach towards curtailing resuscitative efforts if shown to be futile [10]. Team management, including routine pre-resuscitation preparation and structured debriefing are becoming more acceptable practice.

A varying, often significant degree of uncertainty remains regarding most other interventions for and devices used during newborn resuscitation. These include methods of heart rate assessment, incl. pulseless electrical activity [11], resuscitation drugs incl. use of adrenaline (epinephrine) and fluid therapy [12], central vascular access (other than umbilical vein catherization) [13], and supraglottic airways [14], and adjunct technologies, for instance for assessing intubation success and means to measure effective ventilation [15], pneumothorax drainage or ultrasound imaging (ECHO) to assess haemodynamic function during cardiovascular collapse [16].

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Neonatology 2020;117:389–409
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3

Neonatal Oxygen Exposure and Optimal Oxygen Saturations: Do We Have the Answer Yet?

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For 200 years newborn infants in need of stabilization/resuscitation at birth were given 100% O_2. It was not until 40 years ago this practice was challenged, and it took another 30 years before it was changed. In 2010 the International Liaison Committee on Resuscitation (ILCOR), changed recommendations to start with air in term and near term infants and the use of an oxygen blender to use oxygen judiciously in preterm infants. The reason was that multicenter studies and meta analyses had shown excess mortality if the procedure started with 100% O_2. Further, hyperoxia also delayed the time to the first breath approximately 30 seconds [1-3].

However, the last 10 years or so it has become less clear which FiO_2 is optimal to start out with in premature infants < 32 weeks GA and especially the most immature (<28 weeks GA or less) [4].

The following questions are among the most burning in contemporary neonatology:

How much O_2 (assessed by FiO_2, SpO_2) do immature infants need for stabilization the first 5-10 minutes after birth?

What is the optimal SpO_2 increase the first 5-10 minutes of life?

Is there any long term consequences by giving even a brief initial pulse of high FiO_2 ?

Should we start high or low and titrate according to the SpO_2 development?

Data how SpO_2 develops in term non-asphyxic babies the first minutes of life are well established, however data regarding immature babies are much less reliable. Recently we published data demonstrating that for newborn infants < 32 weeks GA there was no difference in outcome whether initial FiO_2 was 0.21 or 1.00. However, for infants < 28 weeks GA mortality is higher if initial FiO_2 is 0.21 compared to 1.00 (RR 3.9 (95% CI 1.1-13.4) [3]. Further, we have shown that infants with GA between 28 and 32 weeks outcome is worse if SpO_2 at 5 min does not reach 80% or more (mortality OR 2.4, 95% CI 1.3-4.4), severe IVH OR 4.5, 95% CI 2.1-9.8) [5, 6]. Although this may reflect that infants not reaching a saturation of 80% within 5 minutes of life is sicker than those who do, recommendations at the present stage is to achieve a SpO_2 of 80-85% within 5 minutes of life.

How and when to adjust FiO_2 to reach this goal is not settled. Data indicate that not before 2-3 minutes of life there is a significant separation in SpO_2 between those who reach and do not reach 80% within 5 minutes of life. This means the clinician has 1-2 minutes only to make proper adjustments. The question is therefore whether it is better to start high, with an initial FiO_2 of 0.6-1.0 or start low with an initial FiO_2 of 0.3. In both cases FiO_2 should be titrated to keep SpO_2 within recommended targets. We know that even a brief pulse of hyperoxia to newborns increases oxidative stress and inflammatory reactions which may last for days and even weeks and perhaps longer. We therefore suggest to start low and titrate FiO_2 up according to the needs. However, this question is presently not yet solved.

Even a brief exposure to 60-100% O_2 also triggers genomic changes. Newborn mice exposed to hyperoxia for days also have epigenetic changes which may last life-long. Exposure to hyperoxia immediately after birth therefore may trigger consequences for adult life and perhaps represent a risk factor for developing degenerative diseases later in life.

Conclusion: The last 10 years the oxygen load to newborns in need of ventilation and stabilization in the delivery room has been reduced substantially. Still, we don't know how premature and especially immature infants should be oxygenated. The consequences of too low or too high oxygen exposure at birth may be life-long. Continuous research in this area therefore is among the most important in present neonatology.

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4

Nasal CPAP: The Gold Standard in Non-Invasive Support

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Despite the many advancements in neonatal medicine, including the widespread use of surfactant, the incidence of bronchopulmonary dysplasia (BPD) has not substantially decreased over the past 10 years. Evidence-based interventions to decrease the

incidence of BPD include vitamin A, caffeine, postnatal steroids and continuous positive airway pressure (CPAP) [1]. Surprisingly, neither surfactant nor antenatal steroids have had a significant impact on the incidence of BPD. The benefits of using CPAP as first line therapy has been demonstrated in multiple clinical trials in which intubation and surfactant have been compared to non-invasive application of CPAP. Meta-analyses from these trials indicate that the use of CPAP significantly decreased the combined outcome of death or BPD [2]. However, the benefits of CPAP are modest with an estimated risk ratio of 0.90 (CI 0.83-0.98). Why has CPAP been only marginally better in the randomized clinical trials? There are four possible reasons. First of all, CPAP looks deceptively simple, but inexperienced usage of CPAP at the centers in the trials may have been a significant contributing factor. Successful implementation of CPAP requires experienced physicians, nurses and respiratory therapists. Data from Aly et al at George Washington University suggest that it may take more than a year after CPAP is introduced to see a reduction in the incidence of BPD [3]. Secondly, many of the infants randomized to the CPAP arm in these trials were intubated and received surfactant when they met failure criteria. Therefore, the trials did not actually compare intubation and surfactant with infants who were successfully maintained on CPAP. Thirdly, the duration of mechanical ventilation was so short in these trials (1-2 weeks) that it would have been difficult to show a reduction in the incidence of BPD. Finally, a variety of CPAP devices were used and the mode of delivery of CPAP may determine its efficacy. CPAP can be delivered using a mechanical ventilator with a threshold resistance exhalation valve, using a bubble CPAP (bCPAP) device or a variable flow nasal CPAP device (e.g., infant flow driver). Small randomized clinical trials suggest that CPAP delivered using a mechanical ventilator may not be as effective as bCPAP or a variable flow device. Gupta et al compared bCPAP with infant flow driver (a variable flow device) and showed that bCPAP decreased the risk of post extubation failure [3]. Experimental animal studies comparing CPAP delivery system suggest that bCPAP increases airway patency improving oxygen extraction and ventilation [4].

Optimal levels of CPAP when used non-invasively are controversial. Observational data from preterm infants suggest that most infants achieve adequate oxygenation with pressures ranging from 4-6 mm Hg. Higher pressures (up to 8 mm Hg) may occasionally be needed, but the safety of higher CPAP pressures is uncertain. Higher CPAP pressures, when used non-invasively) have not been associated with adverse effects on hemodynamics or impaired ventilation. It is important to remember that infants failing CPAP often fail for mechanical reasons related to the CPAP delivery systems and not because of inadequate pressure.

Equally controversial is the best way to wean CPAP. Three weaning strategies have been used, gradual reduction of pressure, sudden removal of nasal CPAP and sprinting. A meta-analysis did not demonstrate the benefit of any one weaning strategy. However, a recent randomized clinical trial by Jensen et al suggested that pressure weans were more effective than "sudden" weans in infants < 28 weeks gestation [5]. Our criteria for weaning include:

- > 30 weeks post menstrual age
- No supplemental oxygen for at least 48 hours
- Asymptomatic PDA
- No bradycardia or desaturation requiring intervention
- ≤ 2 self-limited bradycardia or desaturation episodes in the prior 12 hours
- ≥ 90% saturation in 21% FiO_2
- Free of infection

Conclusions: 1. Preterm infants with RDS weighing < 1500 gms. should be allowed time to demonstrate if they can achieve acceptable ventilation and oxygenation on CPAP. 2. During that time period, these infants must be monitored closely. If ventilation is not improving (pH < 7.2 and PCO_2 > 65) or oxygenation is inadequate with an FiO_2 of 40%-60%, these infants should be intubated. 3. If it is likely that respiratory support with a ventilator will be needed, early administration of surfactant followed by rapid extubation, is preferable to prolonged ventilation (LOE 1).

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5

Limitations of Noninvasive Ventilation: When is Mechanical Ventilation in the Very Immature Infant Indicated?

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Invasive respiratory support in preterm infants is associated with lung injury and increased incidence of BPD. To avoid these complications, several less invasive strategies have been developed to support respiratory function and are now used as an alternative to mechanical ventilation. The oldest and most common modality is Nasal CPAP (NCPAP) that in infants with good respiratory effort has been shown to be as effective as invasive IPPV but with lower incidence of death or BPD. One of the limitations of NCPAP without intubation is that it may prevent the use of surfactant in infants who can benefit from this therapy. In order to provide the beneficial effects of exogenous surfactant and at the same time limit the use of invasive ventilation, many centers use short-term intubation to administer the surfactant followed by rapid extubation (InSurE). The other alternative that has become popular in recent years is the administration of surfactant through a small tube inserted in the trachea while the baby breathes spontaneously while on NCPAP.

Because of the frequent failure of NCPAP in the smaller and sicker infants, an alternative is to use nasal ventilation (NIPPV) instead. This mode of support is more effective than NCPAP, reducing the need of intubation in infants with RDS and significantly reducing respiratory failure and the need for reintubation after weaning from mechanical ventilation. Despite these short-term benefits, the use of NIPPV has not been associated with a consistent reduction in BPD. There are a number of unanswered questions regarding NIPPV, such as mechanisms of action, importance of synchronization, and best indications and settings in different disease states.

Another alternative to NCPAP that has gained popularity in recent years is high flow nasal cannula (HFNC). This method allows oxygen supplementation while simultaneously generating some positive airway pressure. The main advantage of HFNC is that it is simple to use and better tolerated by the infant, but it is less effective than NCPAP. The main limitations of HFNC are the variability in the effective inspired oxygen concentration and in the airway pressure delivered. It is also not possible to accurately measure these values. Both, airway pressure and effective inspired oxygen are determined by the cannula size, the amount of gas flow used, and by the respiratory pattern of the infant.

The use of these less invasive modes of respiratory support is very effective in larger premature infants where it is associated with less need for invasive ventilation and improved outcomes. Unfortunately, in the more immature infants, those under 26-28wks of gestation, the less invasive modalities of support commonly fail and these infants end up requiring invasive ventilation. These are the infants with more severe respiratory failure and with the higher incidence of BPD, but because of the severity of their lung disease, poor respiratory drive and inability to sustain their respiratory effort, fail noninvasive support and still require invasive mechanical ventilation. This partially explains why the incidence of BPD has not decreased in this population.

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Newer Modes of Invasive Conventional Mechanical Ventilation

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Although non-invasive respiratory support is increasingly used in preterm infants, a large proportion needs to be invasively ventilated at some point during their admission [1]. Invasive mechanical ventilation (IMV) may be lifesaving, but may also result in so-called ventilator-induced lung injury (VILI) which is considered an important risk factor in the development of bronchopulmonary dysplasia [2]. Furthermore, IMV can cause significant patient discomfort. Ideally invasive ventilation modes should minimize VILI, by avoiding too high or too low tidal volumes (volutrauma) and limiting the presence of atelectasis (atelectratuma). Furthermore, mechanical support should be synchronized with the spontaneous breathing effort of the infants, thereby improving patient comfort.

Historically, newborn infants have been ventilated with time-cycled pressure limited ventilation (TCPL). During TCPL the end of inspiration is time-cycled, the fixed driving pressure results in a variable tidal volume delivery depending on the lung mechanics and patient effort, and the positive end-expiratory pressure (PEEP) is often set a relatively low level. These characteristics of TCPL may increase the risk of VILI. Newer modes have been introduced to address these limitations.

Volume target ventilation (VTV) modes target a tidal volume instead of a fixed driving pressure, thereby reducing the risk of volutrauma. Studies have shown that VTV improves patient outcomes compared to TCPL ventilation [3]. Proportional assist ventilation modes aim to compensate disease related changes in compliance and resistance and the resulting increased work of breathing. Proportion assist ventilation (PAV) uses flow changes and neurally adjusted ventilatory assist (NAVA) uses electrical activity of the diaphragm to measure the work of breathing and to synchronize the patient effort to the mechanical support [4].[5] Although these modes reduce work of breathing and improve ventilation synchrony, there is insufficient evidence for benefits on important clinical outcomes.

There are several modes under investigation. Airway Pressure Release Ventilation (APRV) applies a high constant distending pressure for a prolonged time combined with time-cycled releases to a lower pressure for a short period of time [6]. Mandatory Minute Ventilation (MMV) supports spontaneous breaths and estimates at regular intervals the minute volume. If the estimated minute volume is below the set target, extra mechanical inflations are started to guarantee the preset minute volume [7]. Variable Ventilation (VV) tries to mimic the variability of VT and respiratory rate observed in normal physiological breathing, which is especially

present in newborn infants [8]. These newer modes have mainly been tested in preclinical studies and are not ready for clinical use.

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7
Minimally Invasive Surfactant Therapy: Useful or Fashionable?

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Minimally-invasive surfactant therapy (MIST; or LISA: Less invasive surfactant administration) is a method to administer surfactant via a thin catheter to spontaneously breathing infants with CPAP (CPAP= Continuous positive airway pressure) support [1]. Randomized controlled trials and meta-analyses have demonstrated that MIST is superior to conventional tracheal intubation or IN-SUR-E (Intubation, Surfactant, Extubation) for surfactant delivery in terms of reducing the need for mechanical ventilation and the combined outcome of death and bronchopulmonary dysplasia (BPD) [2–4]. Maintenance of spontaneous breathing in combination with the MIST strategy holds a big promise in the complex concept of supporting the individual capacity of a preterm infant to adapt to extra-uterine life. Therefore the MIST method meets increasing clinical interest worldwide and is now recommended in international guidelines for surfactant replacement therapy [5]. However, several open questions remain. First, particular indications and treatment thresholds for MIST in distinct patient groups need to be defined and assessed in randomized controlled trials. In particular, strategies of prophylactic MIST for extremely preterm babies < 27 weeks of gestation have been already employed in many units but never been subjected to high-quality trials. Second, unpublished observational data from the German Neonatal Network (GNN) are encouraging in terms of better lung function (FEV1) and intellectual properties (WPPSI score) in MIST treated infants as compared to infants that received surfactant via the standard route. Recent two-year follow-up data from the AMV trial suggest that MIST is a safe strategy, however, the sample size is too small to draw warrant conclusions [6]. More research is needed on long-term outcome after MIST, and five-year follow-up assessments from AMV and NINSAPP trials are under way. Finally, patients' comfort is a strong argument to promote the MIST approach, but it is still connected with the unpleasant experience of laryngoscopy. Therefore positioning during treatment (lateral versus supine?), optimization of devices/catheters to maintain the larynx function, and the issue of analgesia/sedation during the procedure require further study.

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8
BPD, from Pathogenesis to Prevention: An Unresolved Problem

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With the introduction of antenatal steroids, surfactant therapy and modern respiratory support, the original presentation of Bronchopulmonary dysplasia (BPD) described by Northway et al. has become uncommon and has been replaced by a milder form. Most of these infants are not exposed to high airway pressures or inspired oxygen concentrations, the two main insults implicated in the pathogenesis of the original BPD. This milder form of chronic lung illness known as "new BPD", is characterized by a decreased formation of alveolar septae and capillaries and a simplified lung architecture with decreased alveolo-capillary surface.

The prevention of BPD is based on avoiding the multiple factors that contribute to lung injury in preterm infants. The administration of antenatal steroids and surfactant replacement in infants with RDS improves their respiratory course reducing the need for invasive ventilation. Early use of nasal CPAP instead of invasive ventilation has been shown to reduce BPD or death. In infants who still require mechanical ventilation, minimizing volutrauma and exposure to high inspired oxygen concentrations are

important in preventing lung injury and BPD. Volume-targeted ventilation has also been shown to reduce the duration of ventilation and the incidence of BPD. Studies evaluating the use of high frequency ventilation have provided inconsistent results in terms of BPD. The increased risk of BPD in infants exposed to antenatal and postnatal infections stresses the importance of preventing perinatal infections to reduce BPD. Closure of a hemodynamically significant PDA may also play a role in reducing lung injury and the severity of BPD, but the evidence for this is inconclusive.

Supplemental vitamin A administration to maintain normal serum levels has also been shown to reduce the incidence of BPD. The use of corticosteroids in ventilator dependent infants improves lung function allowing faster weaning from mechanical ventilation and supplemental oxygen. However, their use has been associated with worse neurodevelopmental outcome. The optimal population to be treated, age of treatment, dose schedule and duration of therapy have not been clearly established. Recent evidence suggests a reduced incidence of BPD in infants treated with tracheal instillation of surfactant and budesonide early after birth. Some trials have shown a lower incidence of BPD in infants who received hydrocortisone after birth, but this therapy has been associated with higher rates of intestinal perforation.

Caffeine use for extubation and apnea was associated with a reduced incidence of PDA and BPD in preterm infants. The mechanisms for this reduction are not well understood but can be due to a shorter duration of mechanical ventilation in infants receiving caffeine. While the implementation of the interventions described above has resulted in a significant reduction in the incidence of severe BPD, the incidence of milder forms of chronic lung damage remains high.

Future directions in BPD prevention will be targeted to the preservation of normal alveolar and vascular development. Interventions may include the reduction of different mediators that induce inflammation and inhibit alveolar and capillary formation and the possible administration of stem cells as modulators of alveolar and vascular development.

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9
Topical Steroids: Inhaled or Mixed with Surfactant?

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A substantial number of preterm infants around the world (America, Europe, Asia) receive inhaled glucocorticoids for the prevention and/or treatment of Bronchopulmonary Dysplasia (BPD) in routine clinical care despite the lack of data supporting this practice [1, 2, 3]. As a consequence, the Neonatal European Study of Inhaled Steroids (NEUROSIS) that investigated the role of inhaled budesonide for the prevention of BPD was launched. NEUROSIS showed a significant reduction in the incidence of BPD [4]. However, the primary outcome (a composite of death or BPD at 36 weeks postmenstrual age) was only of borderline significance as a result of a non-significant trend to increased mortality in the budesonide group [4]. Neurodevelopmental disability among survivors at a corrected age of two years was a predefined secondary outcome [5]. At the time of the follow-up examination, this long-term outcome, was 48% in the budesonide and 51% in the placebo group (RR: 0.93; 95% CI: 0.80, 1.09; $P = 0.40$) but post hoc results suggested higher mortality with budesonide [5]. No plausible explanation had been identified after a detailed review of the causes of death and clinical course of all study infants who died [4, 5, 6]. In the analyses, no adjustment was made for multiple comparisons [5].

In a systematic review, all studies in which inhaled glucocorticoids were compared to placebo for the prevention or treatment of BPD in preterm infants were pooled in various meta-analyses [7]. In the inhaled glucocorticoid group, there was a significant beneficial effect on the incidence of BPD at 36 weeks and no effect on mortality [7]. The authors of the systematic review concluded that inhaled glucocorticoids may be considered for the prevention or treatment of BPD [7].

Delivery of glucocorticoids to the periphery of the lungs may be facilitated by the aid of other drugs, e.g. by surfactant used as a vehicle. In a pilot trial with 116 newborns, Yeh and colleagues treated neonates every 8 hours with either 0.25 mg/kg of budesonide mixed with 100 mg/kg of surfactant or surfactant alone [8]. Inclusion criteria were very low birth weight (less than 1500 g) and severe respiratory distress with a fraction of inspired oxygen ≥ 0.6. The researchers could demonstrate that the combined therapy with budesonide and surfactant improved the composite outcome of BPD and death.

In the largest RCT published today, the mixture of surfactant and budesonide decreased BPD by 21% with a significant effect only seen for severe BPD when using the NICHD definition [9]. No acute adverse effects and no effect on neurodevelopmental outcomes at 2-3 years were reported [9].

In a recent observational study, two time periods were compared in a single center. In the more recent time period, a local clinical practice change was introduced to include budesonide with surfactant in clinical care. BPD or death did not change between the historical surfactant cohort and the budesonide cohort. However, budesonide was associated with decreased severity of BPD, decreased mechanical ventilation use, earlier discharge, and similar short-term outcomes [10]. Although the published results from controlled clinical trials combining surfactant and glucocorticoids are promising, they should be replicated in large RCTs performed in different settings and countries.

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10
Why Do Former Preterm Infants Wheeze?

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Longer term respiratory morbidity is a frequent concern for former preterm infants. Increased airway reactivity and wheezing disorders are extremely common in this population, both in infants who meet diagnostic criteria for bronchopulmonary dysplasia [BPD], and in the absence of this diagnosis. It is, therefore, imperative to gain a better understanding of normal and abnormal postnatal development of the immature airway. Airway hyperreactivity may be secondary to abnormal bronchoalveolar attachment in the face of parenchymal lung injury, or secondary to an imbalance between constrictor and dilator neural pathways. Finally, the airway itself may undergo functional and/or structural changes, including increased airway smooth muscle mass, and changes in airway extracellular matrix which may, in turn, modulate downstream signaling pathways to hyperoxia or pressure exposed vulnerable airways.

In order to characterize biologic mechanisms that contribute to airway hyperreactivity in former preterm infants, we and others have employed neonatal rodent models that are both immature at birth and readily survivable. Of interest is the observation that even modest exposure to oxygen [e.g., FiO_2 of 0.4] can cause greater airway hyperreactivity than severe hypoxia [FiO_2 of 0.7] as the latter can result in apoptosis rather than hypertrophy of airway smooth muscle [1]. Application of CPAP to the neonatal mouse model also may contribute to increase airway wall thickness and enhanced contractility [2, 3]. A novel new line of investigation is the role of altered extracellular matrix in the airway and surrounding tissues in modulating airway smooth muscle signaling [4].

There is, unfortunately, no evidence that the persistently impaired airway function exhibited by former preterm infants is diminishing, despite increased use of non-invasive ventilatory strategies [5]. It is unclear how much is contributed to by structural versus functional consequences of preterm birth on the immature airway. Meanwhile, we must minimize exposure of former preterm infants to adverse environmental influences such as smoking, as impaired airway function persists well into adulthood in this high risk population.

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11
Follow-Up and Long-Term Respiratory Function After Premature Birth

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Bronchopulmonary dysplasia (BPD) is the most frequent respiratory complication of extremely premature birth. As most preterm-born infants survive and reach adulthood nowadays, we should start acknowledging preterm birth as a chronic condition that requires long-term follow-up. Data from major cohort studies demonstrate that low gestational age and birth weight are inversely

associated with mortality from infancy to mid-adulthood, with a higher risk of cardiorespiratory diseases [1]. Prematurity is characterized by an immature stage of lung development. Various injuries before and after birth, together with a genetic susceptibility, can lead to direct airway and parenchymal damage, inducing a deviation from the normal developmental path [2]. Depending on the timing and extent of exposure, lung injury may range from early developmental arrest to structural damage of a relatively immature lung [2], involving smaller airways and lower than normal lung volumes [3]. In most studies, survivors of BPD have airflow limitation and their FEV1 (a powerful indicator of flow limitation on spirometry) does not reach the normally-expected optimal peak at 24 years old [4]. Poor lung function early in life tracks with a weaker lung function in adulthood, and a higher risk of a COPD-like disease [2, 5]. In a recent Australian study, preterm infants showed a worrying decline in spirometric values over time, with the worst trajectories in BPD survivors [6]. Histopathological findings in adolescent BPD survivors confirm BPD as an active disease with ongoing airway inflammation [7]. Although the young people affected are often treated as asthma patients, the two obstructive lung diseases do not share the same pattern of inflammation.

A key aspect of better care for extremely preterm babies with lung problems is a structured and standardized cardiopulmonary follow-up at ambulatory care clinics, identifying the relevant elements of clinical care, as well as markers of health and disease [8]. There are few current recommendations on the long-term monitoring and treatment of these children, based largely on a low quality of evidence. The European Respiratory Society advocates urgent studies to assess the effectiveness of bronchodilators, inhaled corticosteroids, diuretics and macrolides in BPD survivors after discharge [9]. Standardized lung function tests may be useful for understanding changes over time and guiding treatment options, but measuring lung function in early life is challenging. Spirometry with lung volume and diffusion capacity measurements can be performed in older children (from 5 years on) [8].

Since preterm birth may be a previously-underestimated risk factor for heart failure in children and young adults, a closer follow-up and assessment of this population's cardiac health may be necessary.

All in all, the most effective strategy for preventing long-term respiratory and cardiac morbidities in these subjects would be to reduce the burden and severity of BPD, and to identify its early predictive biomarkers to guide new treatments. Despite advances in neonatal intensive care, current strategies (antenatal corticosteroids, surfactant therapy and noninvasive ventilation) are scarcely effective in preventing BPD. In recent years, treatments with mesenchymal stem cells and their secreted extracellular vesicles have shown promise [10, 11].

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12
The Microbiome and the Developing Immune System

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The infant's microbial colonization of internal and external surfaces - including the gastrointestinal tract, skin, and oral mucosa - is established in a complex, dynamic, and step-wise process and will eventually establish a mutualistic relationship with the host's mucosal and systemic immune systems. Both maternal and neonatal factors influence in a quantitative and qualitative fashion the bacterial colonization and consequently the maturation of the immune system, whereby, for example, the mode of delivery, breastfeeding, and antibiotics used perinatally as well as gestational age have been shown to impact on the richness and diversity of the intestinal microbiome. This colonization occurs during a critical developmental window and coincides with a possibly time-restricted phase during which the plasticity of the mucosal immune system predisposes to receive microbial instruction as to its own differentiation and functional maturation. This interaction is initiated within hours after birth and involves originally pioneering microbiota of relatively low diversity thought to facilitate bi-directional host-commensal interactions that establish the immune system's maturity including its tolerance to environmental exposures. Indeed, the absence of commensals has profound effects on the structural and functional development of the immune system, including but not limited to defects in lymphoid tissue development within the spleen, thymus, and lymph node. The early life environment also likely determines, at least in part, the

microbial composition and complexity in adult life, and when disturbed may contribute to the development of microbial states that have been associated with disease later in life, including inflammatory bowel disease, allergy, and asthma. The presentation will review recent findings of the instructive relationship between the intestinal microbiome and the immune system of the neonates.

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13
Platelet Transfusions: More Harm than Benefit?

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Thrombocytopenia in newborn infants admitted to neonatal units is common and transfusion of donor platelets to keep the platelet count at a safe level to prevent bleeding is frequent, but to now there has been little evidence to define what platelet count is 'safe'. There are also international differences of opinion on what platelet threshold should be used as an indicator for prophylactic platelets to be given. A single study, in 1993, randomised preterm infants to receive prophylactic platelets at a threshold of either 150×10^9/l or 50×10^9/l, with no difference in bleeding between the two groups [1]. This set 50×10^9/l as the default 'safe' threshold adopted in the USA, though a more restrictive use of platelets, based on lower thresholds, is more common in Europe [2]. While platelet transfusion to prevent bleeding is mandatory in some aetiolgies, eg. fetal and neonatal alloimmune thrombocytopenia (FNAIT) and generally unnecessary in others, eg. autoimmune thrombocytopenia (ITP), the commonest causes of a low platelet count, placental insufficiency and infection are not necessarily associated with a significant bleeding tendency.

Two recent multicentre studies in the UK have provided evidence to define the relationship between platelet count and bleeding risk, and establish an appropriate prophylactic transfusion strategy.

The PlaNeT-1 study was a prospective observational cohort study in seven regional neonatal intensive care units, which documented platelet counts and bleeding episodes in all babies whose platelet count fell below 60×10^9/l [3]. The major findings were that only 9% of infants whose platelet count fell below 20×10^9/l developed bleeding classified as severe, though some minor bleeding was common. The novel finding was that major haemorrhage was more associate with gestational age <28 weeks and a platelet count $<50 \times 10^9$/l within the first 10 days. There was no evidence that minor bleeding predicted the development of major haemorrhage.

This observational study was followed by a randomised therapeutic study, PlaNeT-2, comparing bleeding and mortality in infants born at less than 34 weeks, randomised to receive prophylactic platelets below a threshold of either 50×10^9/l or 25×10^9/l. [4]

Infants were enrolled with parental consent following a recorded platelet count <100 3 10^9/l. Of 1,029 enrolled infants, 660 (64%) developed thrombocytopenia <50 3 10^9/l. These were randomised equally between the higher and lower threshold groups. In the higher threshold group, 90% received at least one platelet transfusion; in the lower threshold group, 53% received at least one transfusion.

The primary outcome was death *or* major bleeding up to and including day 28. A primary outcome event occurred in 26% of high threshold subjects and 19% of low threshold subjects (P=0.02). There was a significantly higher mortality in those infants randomised to receive platelets at the higher threshold of 50 3 10^9/l, compared to the lower threshold of 25 3 10^9/l (15% v 10%). There was no significant difference in the incidence of bleeding (major or minor) between the two groups.

This large randomised study has provided objective evidence that a more restrictive platelet transfusion policy, with a prophylactic transfusion threshold of 25 3 10^9/l, is safe and does not incur a greater risk of major haemorrhage. However, the study unexpectedly found a higher mortality in infants randomised to the higher threshold and who consequently received more platelets. This unexpected finding is unexplained, but poses the question as to why more platelet transfusions might tip the balance to greater harm than benefit.

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Further Reading

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14
An Evidence-Based Approach to Neonatal Sepsis: Finding a Needle in a Haystack

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Despite the many advancements in neonatal medicine, the management of infants with suspected early onset sepsis remains a conundrum. Because of the potential risks of increased morbidity and mortality, many clinicians choose to treat infants with

antibiotics, even when the probability of sepsis is considered low. Unfortunately, the indiscriminate use of antibiotics in the first few days of life has been associated with increased mortality (especially with the use of 3rd generation cephalosporins) and dysbiosis, (which may predispose preterm infants to bronchopulmonary dysplasia, necrotizing enterocolitis and late onset sepsis). Furthermore, sepsis workups are costly, increase the duration of hospitalization and interfere with breast feeding and maternal bonding. The traditional approach to sepsis workups involves an assessment of risk factors and a careful physical examination. Symptomatic infants with risk factors are almost always treated with broad spectrum antibiotics. The greatest challenge is deciding how to manage infants with suspected sepsis who look well, but who have risk factors for early-onset sepsis (e.g., chorioamnionitis). Guidelines, which recommended treating every infant exposed to maternal chorioamnionitis, led to overtreatment of infants who were not infected. In late preterm and term infants born to women with chorioamnionitis, the risk of sepsis is about 1%. If the infant is well-appearing at birth, the risk of sepsis is considerably lower.

The American Academy of Pediatrics, Committee on the Fetus and Newborn has recently recommended three strategies for the evaluation and management of infants ≥ 35 weeks gestation with suspected early onset sepsis [1]. They preface the recommendations with four guiding principles:

- No single method can be used to identify all infants with early-onset sepsis with precision
- Each strategy has merits and limitations
- Each strategy must include measures to monitor the infant and minimize the duration of antibiotic therapy
- Birth centers should choose a strategy that is best suited to their local resources.

The first strategy called categorical risk assessment uses risk factor thresholds to identify infants with early onset sepsis. This approach recommends treatment of any infant born to a woman with chorioamnionitis or who is ill appearing. The limitations of this approach are: 1) No clear definition is provided for clinical illness, 2) It overlooks the difficulty in establishing an accurate diagnosis of maternal chorioamnionitis, 3) inconsistent consideration is given for intrapartum antibiotics, and 4) no clear guidelines are given for an abnormal laboratory test.

The second strategy called multivariate risk assessment uses a sepsis calculator to define risk. This is the most popular approach in the United states. The risk of sepsis is calculated based on historical risk factors and clinical signs and the incidence of sepsis. Management is based on the estimated incidence (expressed per 1000 live births). The limitations of this approach are: 1) the sepsis calculator will miss a substantial portion of infants with proven sepsis (~30%), 2) Infants with an equivocal presentation and a calculated incidence of sepsis ≥ 1/1,000 live births but < 3/1,000 live births require a blood culture, but blood cultures have a poor sensitivity in that setting and 3) the definition of an equivocal presentation is likely to overlap with that of a well-appearing infant depending on when the physical examination is done.

The third approach employs serial observations without testing in infants who are well-appearing but born to women with risk factors for sepsis (including chorioamnionitis). When the infant becomes symptomatic, antibiotics are initiated. The limitations of this approach are: 1) there are limited data to support this approach, 2) the hospital has to develop systems to do serial observations and record them accurately and 3) the assessments will add the cost of well newborn care.

Recommendations: 1. Babies with clinical signs of early onset sepsis should receive broad spectrum empirical antibiotics. 2. Well appearing late preterm and term infants can be closely observed without empirical antibiotics or evaluated using the sepsis calculator. 3. Limit the duration of antibiotic therapy (36hours) in infants who are clinically improved with negative blood cultures.

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15
How Can We Reduce Brain Injury in Preterm Infants?

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Premature birth carries significant long-term risks. While mortality has been consistently falling even for the most immature infants, there is less sustained improvement in neurocognitive outcomes: about 10% of survivors develop cerebral palsy; around one third have definable cognitive problems; and there is an increased rate of many mental health problems, for example a 7x increased risk of bipolar disorder.

The underlying brain injuries that leads to these long-term problems are poorly understood. Accounts of preterm brain injury tend to emphasise lesions detected at post-mortem examination or by neuroimaging such as intraventricular haemorrhage, parenchymal infarction, and periventricular leukomalacia. However, the population incidence of these injuries is too low to account for the incidence of neurocognitive deficits. Consequently, conventional neuroimaging is only partially successful in detecting infants who will grow up with long-term problems.

Some of this 'diagnostic gap' is due to factors operating beyond the perinatal period, and social deprivation is a potent predictor of adverse outcomes. Nevertheless, there is now much interest cerebral dysmaturation after preterm birth, particularly associated with inflammation and oxygen dysregulation.

Advanced computational imaging has shown a wide range of abnormalities in preterm brain growth: thalamic and cortical growth in particular are reduced, and white matter and cortical microstructure are affected. These abnormalities are widely different between infants, and it is clear that some of these changes begin before delivery, while genetic imaging methods have discovered genetic predispositions to abnormal brain development.

Preterm brain injury is thus complex and poorly understood. Experimental and pathologic evidence shows that maturation of pre-oligodendrocytes, growth of axons, dendritic arborisation and synaptogenesis are all impaired, and that microglia play an important role both in modulating normal brain development and in mediating effects of inflammation. Microglia are involved in

normal synaptogenesis and in synaptic pruning, and there is increasing evidence that they may play a central role in preterm brain dysmaturation.

To date specific interventions that reduce adverse outcomes have modest effects. Outcomes can be improved by some therapeutic interventions, including maintaining appropriate oxygen saturations, magnesium administration before delivery and caffeine given after birth. Reducing ex utero transfers of infants reduces the incidence of focal brain lesions. Promising interventions such as erythropoietin are under investigation, and there are interesting possible benefits to be had by optimising nutritional and environmental effects in the neonatal period.

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Monitoring the Neonatal Brain: How, When and For How Long?

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There is an increasing interest to monitor the neonatal brain. In the *full-term infant* who receives hypothermia for neonatal encephalopathy due to presumed perinatal asphyxia, some centres will use amplitude integrated EEG (aEEG) as part of the entry criteria for cooling. Most will use aEEG during cooling and rewarming and an increasing number of centres are now also using continuous video EEG. [1] Several seizure detection algorithms have become available, improving recognition and allowing for appropriate treatment. Continuous use of the EEG will confirm the effect of antiepileptic medication and will recognize ongoing electrographic seizures, following uncoupling. [2] Combining aEEG with Near Infrared Spectroscopy (NIRS) allows prediction of neurodevelopmental outcome earlier than the use of aEEG only. [3]

In the preterm infant continuous EEG and NIRS are not yet standard of care and are used in neuro-dedicated centres. The incidence of seizures is not yet clear and whether and how to treat them is not yet well elucidated. [4] Reduced NIRS values during the first 72 hours is predictive of neurodevelopmental outcome. [5]

For both the preterm as well as the full-term infants, neuroimaging should also be seen as monitoring the brain. In the full-term infant with perinatal asphyxia receiving hypothermia and any infant with neonatal seizures, MRI should be performed following bed-side ultrasound. [6] In the preterm infant, cranial ultrasound is preferred for monitoring development and evolution of brain injury. Especially in preterm infants who develop post-hemorrhagic ventricular dilatation (PHVD) close monitoring with ultrasound is indicated and will guide timing of (neurosurgical) intervention. [7] At least one MRI at term equivalent age should be considered in those with abnormalities recognized on ultrasound and the extremely preterm infant with a GA<28 weeks. Several studies have now shown that imaging findings at term equivalent age predict school age outcome. [8]

Conclusion: Neuromonitoring should become routine clinical care and will play an important role in measuring the effect of neuroprotective interventions.

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17
Analgesic Drugs: Impact on Pain Perception and Brain Activity

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Pain experienced during infancy can have long-term negative consequences, but is under-treated and poorly understood, representing a significant clinical problem. For an infant who requires hospital treatment, medical procedures are an everyday reality, and the youngest and sickest infants may experience more than 50 procedures per day [1]. Nevertheless evidence-based analgesic treatment options are limited and understanding of the mechanisms that underpin the development of pain perception is poor [2]. In this lecture, I will discuss how we can better understand how the human infant central nervous system develops to enable us to experience and modulate pain, and to use this understanding to develop new analgesic treatment options for infants.

One approach to solving these research challenges is to combine clinical neuroscience with novel analytical methods to improve understanding of infant brain development, and to translate this knowledge into the design of new clinical trials to test the analgesic efficacy of pain treatments. This is an important step, because until relatively recently, this field was characterised by outdated dogma (based on a misplaced historical perspective that

infants cannot feel pain). However, recent scientific and technological advances in human imaging provide an opportunity to gain insight into how immature structural and functional brain architecture influences the development of pain-related brain activity and behaviour [3, 4].

Using near-infrared spectroscopy, functional magnetic resonance imaging (fMRI) and electroencephalography, I will show how we can use these methodological approaches to measure pain-related brain activity in infants [5]. I will describe fMRI studies in newborn infants that show that evoked patterns of pain-related brain activity are similar to adults, with brain areas associated with emotional aspects of adult pain also active in infants. I will discuss how this work has led to the development of brain-derived measures that are validated in both premature and term-born infants, sensitive to analgesic administration, and which have been used in a clinical trial to assess the analgesic benefits of pharmacological interventions [6]. A direct example of how this work can lead to healthcare benefits will be highlighted in the Poppi (Procedural Pain in Premature Infants) trial, where we established that the use of oral morphine at a dose of 100 μg/kg (a dose recommended in current national formularies and used clinically on our neonatal unit) is not appropriate to treat pain evoked by retinopathy of prematurity screening in non-ventilated infants [7].

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The Use of Opioids in the NICU: Navigating Between Scylla and Charybdis

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Analgesic dosing regimens including the choice of drug (e.g., opioids, acetaminophen, NSAIDs) should take into account the severity and type of pain, the therapeutic window of the analgesic, but also the age or developmental state of the (pre)term newborn [1-4]. Translation of these concepts into safe and effective pharmacological analgesia in neonates necessitates thorough understanding of the principles of clinical pharmacology. Growth, weight or size and maturation or age evolve and profoundly affect pharmacokinetics (concentration-time profile, absorption, distribution, metabolism and excretion) and pharmacodynamics (concentration-effect profile, objective assessment).

Inadequate management of pain in (pre)term neonates alters and affects thresholds of pain, pain or stress-related behavior, physiological responses, and contributes to impaired neurodevelopmental outcome [5].

Alterations in biological covariates (e.g. peripheral and central somatosensory function and modulation, brain structure and connectivity) and psycho-social covariates (e.g. gender, coping style, mood, parental response) that affect pain perception and expression were identified in former preterm neonates [5]. Consequently, effective analgesia is relevant not only because of ethical reflections or human empathy, but it is a crucial and integral part of medical and nursing care to neonates.

In the (pre)term newborn, it seems that the limbic system hereby has a specific vulnerability for overexposure to pain, stress or drugs (narcotics, analgesics, or sedatives). This is likely because the maturational changes in the limbic structures evolve at a very fast rate throughout the last trimester of pregnancy until late infancy. The limbic system, hippocampus and the regions connected to the hippocampus are essential as switch board to encode, consolidate and retrieve memory. Intriguingly, these types of memory deficits are frequently observed in former preterm neonates [6].

However, there is also emerging evidence on the relation between the exposure to narcotics and impaired neurodevelopmental outcome, resulting in a Catch-22 scenario [6]. Experimental data from animals provide evidence that chronic morphine exposure in perinatal life results in a reduced brain volume, decreased neuronal packing density, and less dendritic growth and branching. This is associated with learning and motor disabilities. It is, however, currently too early to blame these findings purely on the use of opioids [7].

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Preventive Strategies, Prediction and Up-To-Date Treatment of Severe ROP

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Retinopathy of prematurity (ROP) is a major cause of preventable blindness worldwide. Preventive strategies aim to promote normal growth of retinal blood vessels through oxygen control, optimisation of nutrition including critical long chain polyunsaturated fatty acids arachidonic acid and DHA, provision of raw maternal breastmilk [1] and preservation of fetal haemoglobin [2]. In addition, the role of the beta-blocker propranolol in preventing progression of ROP is investigated [3].

With current ROP screening less than 10% of screened infants need treatment [4]. Prediction models based on birth characteristics, postnatal weight gain and other factors have been developed to reduce examinations in low-risk infants. A model based on advanced statistics using birth characteristics only, from more than 7000 infants registered in the Swedish ROP registry (SWEDROP) has recently been published and appears to predict total risk of ROP-treatment as well as models including weight measurements [5]. Surprisingly, treatment risk peaked at 12 weeks of age independent of gestational age at birth. Another new validated prediction model based on daily weight gain demonstrated high sensitivity suggesting a 30% reduction in the number of infants needing screening [6]. Based on ten-year SWEDROP data [7] screening will be changed in Sweden 2020 to include only infants with a gestational age of <30 weeks and to postpone the first examination to 6 weeks postnatal age in infants born at > 26 weeks. This will reduce the number of infants screened in Sweden with approximately 20%.

Laser therapy is the method of choice for severe ROP. Anti-VEGF therapies are implemented worldwide despite insufficient knowledge of choice of drug, dosage and long term systemic effects. There are still concerns regarding the systemic effects on comorbidities and neurodevelopmental outcome with the use of Anti-VEGF [8, 9]. In the multicentre Rainbow trial the effects of the Anti-VEGF drug Ranibizumab (Lucentis®) on ROP treatment were compared with laser without demonstrating any significant differences [10]. There was a trend for Lucentis superiority regarding favourable ocular outcomes although with a higher risk of recurrence. Lucentis was approved for the indication of treating severe ROP in October 2019. Long-term follow-up of the Rainbow study is on its way.

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Hypoxic-Ischemic Episodes: A Hidden Risk for Brain Damage of Very Immature Preterm Infants?

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Non-invasive, continuous oxygen monitoring, with its origins in the mid-1970s, first allowed us to document the high incidence of intermittent hypoxic [IH] episodes. However, it is only over the last decade that increasing attention has been drawn to the potential longer term consequences of IH [1]. It is now clear that the magnitude of these episodes results from a combination of immature respiratory control superimposed upon an immature lung.

Immature neural maturation that characterizes preterm birth can be adversely impacted by IH in various ways. One example is retinopathy of prematurity [ROP] where unique characteristics of hypoxic episodes play an important contributing role [2]. Another is the potential longer term effects of IH in the neonatal period on sleep disordered breathing in former preterm infants [3]. Elegant neonatal rodent studies clearly support a longer term effect of IH on stability of respiratory control.

Persistence of apnea of prematurity has consistently been associated with poor neurodevelopmental outcome. While such associations are not necessarily causal, an increasing body of evidence is emerging. Poets has documented that prolonged hypoxic episodes of at least one minute's duration were associated with adverse 18 month outcomes [late death or disability, including ROP] [4]. We have observed that shorter IH events of at least 20 seconds' duration adversely impacted survival, especially in the face of intrauterine growth restriction [5]. A high incidence of IH events also predicts subsequent development of bronchopulmonary dysplasia [BPD], a well-known association of neurodevelopmental disability [6].

There is, therefore, a compelling need to characterize which components [duration, magnitude, incidence and timing] of IH

are predictors of adverse outcomes. Similarly, the underlying mechanisms [oxidative and/or inflammatory pathways] need to be elucidated if appropriate intervention strategies can be initiated.

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Neonatal Jaundice: A Puzzle Still Unresolved

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Neonatal jaundice (NNJ) is perhaps the neonatal transitional process that most commonly requires medical assessment and therapy [1]. Factors that increase unconjugated bilirubin (UCB) production, or inhibit/delay its hepatic excretion, may cause pathological jaundice [2]. Very elevated serum UCB (TSB) levels can lead to severe brain damage, kernicterus spectrum disorder (KSD) [3]. KSD is rare in industrialized countries, but now often involves infants discharged from the nursery whose readmission to hospital for emergency NNJ treatment was delayed. In LMICs KSD remains one of the most common causes of brain damage in newborn infants [4]. NNJ was described centuries ago, but many aspects of NNJ and its treatment remain "a puzzle still unresolved".

UCB is at the same time both a physiologically important antioxidant and a potential toxin [5, 6]. We really do not know how these two characteristics balance or compete in brain. UCB is potentially toxic to the brain because in its predominant isomeric form in serum, IXα (*Z,Z*), it behaves as lipid soluble and is able to cross the blood-brain barrier (BBB) and enter the brain [7]. However, its brain entry appears to be modulated by membrane transporters, and we need to learn more about the identities and characteristics of these 'flippases', particularly whether such transporters could be pharmacologically upregulated to impede UCB entry into, or facilitate its clearance from, brain [8].

Inhibitory effects of UCB have been found in many biological systems and reactions, but there is no agreement on 'the basic mechanism of UCB toxicity'. Inhibition of protein phosphorylation is a common theme in many reactions inhibited by UCB (7), but UCB could also be a 'promiscuous inhibitor' and the many in vitro observations may not reflect what goes on in vivo [9]. Identifying a basic mechanism might open the door to rescue interventions in infants acutely threatened by UCB neurotoxicity.

Phototherapy (PT is the most common therapeutic intervention in NNJ, converts UCB to more polar isomers, and lowers TSB by facilitating UCB excretion into bile and urine. However, conversion of UCB to photoisomers (PI) may have another salutary effect beginning as soon as PT starts [9]. Because PIs are water soluble they should be less able to cross the BBB than IXα (*Z,Z*), thus potentially creating an equilibrium shift to drive UCB out of the brain. This hypothesis makes theoretical sense, but still needs in vivo experimental verification. Side effects of PT have been reported, both short- and long-term, which point to the need for more studies to clarify the relative roles of irradiance, spectral power, duration, and wavelength as far as optimizing the therapeutic effect while minimizing side effects/toxicity.

UCB oxidation may contribute to its clearance from brain [8, 9], but we need to identify the enzyme(s) as well as to verify whether the oxidation products are non-toxic. Several genetic variants modulate production and excretion of UCB and thus influence the risk for KSD [10]. Testing for genetic risk may need to become part of a comprehensive pre-discharge risk evaluation that should probably also include aspects of the health care delivery system and its preparedness for 'crash cart' management of infants with extreme NNJ. These aspects also need further study.

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Outcome into Adulthood for Our Most Immature Infants

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Over the past 25 years we have seen an explosion in what we understand about long term outcomes particularly for the extremely preterm individuals now entering adult life. Although much is centred on neurodevelopment, prematurity is a pervasive problem for development affecting multiple organ systems both in the neonatal period and subsequently, and the implications for adult life are only now becoming apparent. Pioneering work by Maureen Hack [1] and Saroj Saigal [2, 3] is now maturing as we start to understand the implications of our childhood observations and impact that very preterm or extremely preterm birth has on the survivors.

We have followed the EPICure cohort of individuals born in 1995 at less than 26 weeks of gestation through to 19 years of age. The use of longitudinal data allows the determination of trajectories for the evolution of a range of functions. Using statistical methods to account for loss to follow up we can demonstrate that from 6 to 19 years cognitive scores remain remarkedly constant and do not show significant change as the children grow up or in relation to reference scores. [4] Work from the Bavarian Longitudinal study of very preterm children shows similar findings but the trajectory of preterms appears less variable than that of term controls. [5]

The preterm child has a common behavioural phenotype, namely a constellation of inattention, internalising behaviours and deficits in social cognition. [6] Although these appear much greater at school age, by adult life (and using self-report) differences as young adults appear to be less. [7] Nonetheless the population prevalence of psychiatric disorders related to this phenotype, namely anxiety, depression, ADHD, and ASD appear to be elevated in preterm populations in a dose dependent fashion. [8]

Cognitive impairment over school age leads to lower levels of attainment and qualifications as a group, with fewer individuals graduating from college. In turn this leads to lower paid positions and reduced lifetime wealth. However, much of the differences seen in comparison to term-born peers may be explained by the excess of neurosensory impairments found in these now historic populations. [3] In addition, the behavioural phenotype mitigates against high peer pressure leading to fewer risk-taking behaviours, such a recreational drugs, smoking and alcohol leading to lower degrees of sociopathy.

Further work is required to establish the effect on other organ systems, such as the respiratory and cardiovascular systems, and to understand the implications of these findings for ageing.

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Preterm Nutrition in 2020: Breast Milk, Probiotics and Other Components

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The mainstay of preterm nutrition in 2020 is a baby's mother's own milk. But other than for this universal agreement, there is controversy about almost every other aspect. There are many questions that urgently need to be answered. Should pasteurised human donor milk or formula be used if there is insufficient mother's milk? Does mother's milk require routine macronutrient fortification? Do probiotics and bovine lactoferrin protect against necrotising enterocolitis (NEC) and sepsis? Should preterm formula be enriched with long-chain polyunsaturated fatty acids? Do very preterm babies require nutrient enriched follow-on formulae? Sadly, we still do not have reliable answers to any of these questions.

In preterm infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or sole diet, does not show an effect on all- cause mortality, or neurodevelopment [1]. Two large well conducted randomised controlled trials (RCT) of bovine lactoferrin have failed to confirm promise indicated by a meta-analysis of small studies [2]. Current evidence does not support the use of human milk fortification [3], nutrient enriched post-discharge [4], protein hydrolysate [5] or LCPUFA- supplemented formula [6].

A 2014 systematic review and meta-analysis concluded enteral probiotics reduces severe NEC and all-cause mortality in preterm infants though noting that RCT were highly variable with regard to birth weight, gestational age, baseline risk of NEC, timing, dose, probiotic strain and feeding regimen [7]. To-date enteral probiotics have been evaluated in over 46 RCT, all but two [8, 9] of which were small and underpowered to detect important outcomes. Of the two large RCT, the ProPrems trial involving *Bifidobacterium infantis*, *Streptococcus thermophilus* and *Bifidobacterium lactis* showed no difference in the primary outcome, sepsis [8], or all-cause mortality but did find a reduction in the secondary outcome NEC (Bell stage 2 or more). The second large trial, PiPs, with the *Bifidobacterium breve* showed no significant difference in the three primary outcomes, NEC (Bell stage 2 or more), sepsis and all-cause mortality [9]. A 2017 review of 29 probiotic RCT [10] found NEC

was often reported as a secondary or composite outcome. This is an important consideration because secondary outcomes are prone to both type one ("false positive" results) and type two errors ("false negative" results). Trials are usually designed to have statistical power to detect a difference in the primary outcome but are underpowered to detect differences in secondary outcomes. Reporting many secondary outcomes increases the risk that a "statistically significant" *p*-value will be identified by chance.

What can be done to resolve these important, continuing uncertainties? The plethora of "expert-opinion" or "consensus-opinion" based guidelines are unhelpful. Indeed they risk harming babies by the universal imposition on all infants of clinical practices that are not evidenced based. There are many lessons from the past that should have taught us the dangers of care dictated by expert opinion, rather than evidence. The only rational way forward is for neonatologists to collaborate to test these uncertainties in high-quality, properly powered, international RCT.

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Essentials and Pitfalls of Parenteral Nutrition

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During the first weeks of life, premature neonates are at highest risk of developing nutritional deficits. These nutritional deficits may reach a daily shortage in energy and proteins in comparison to the recommended dietary intake [1]. Providing essential nutrients to low birth weight infants during the early postnatal period is critical for adequate growth and neurodevelopment. Malnutrition in all kinds of species leads to neurodevelopmental impairment but slow growth (which does not equal malnutrition) is related to longevity [2, 3] Reduction of malnutrition rates results in higher postnatal growth rates and is associated with favorable long term neurodevelopmental outcome [4–6]. Supplementation of amino acids has shown to improve protein balance by increasing protein synthesis, improves anti-oxidant defense system [7] and can potentially prevent catabolic state and neonatal growth retardation [8]. On the other hand, studies in critically ill neonates, older children and adolescents have shown that parenteral nutrition during the first week may result in adverse outcomes, such as an increase infections and in ventilation days [9, 10]. Especially the provision of amino acids increased the likelihood of acquiring a new infection, while the likelihood of earlier live weaning from mechanical ventilation and the likelihood of earlier live PICU discharge was lower. By contrast, more glucose during the first 3 days of PICU stay was independently associated with fewer infections. Risk of harm with amino acids was also shown for low doses. This has led to a shift in the thoughts about providing parenteral nutrition, although these results have only been shown in term infants. Nevertheless, the most recent guidelines, published by the ESPGHAN, ESPR and ESPEN and the Chinese brand of the ESPEN have worded their recommendations more carefully than the previous ones, stating that for term infants withholding parenteral nutrition during the first week may be considered [11]. A similar trial in preterm infants is not yet planned. The question is whether stable preterm infants benefit from withholding parenteral nutrition; most likely they do not. However, in case of severe and acute NEC or severe sepsis, one can consider withholding especially amino acids also for preterm infants. Amino acids may hamper autophagy during critical illness which in its turn may worsen hepatic mitochondrial damage and dysfunction [12]. Again, it should be stressed, no data are available to support this hypothesis in preterm infants, neither is there any insight to for as long such a period should last. A large multicenter trial should be planned to answer this important question.

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How to Manage Postnatal Growth Failure?

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According to the American Academy of Pediatrics, "Current recommendations for parenteral and enteral nutrition are designed to provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients." Unfortunately, most preterm infants do not grow after birth for many days, even after early postnatal water balance adjustments in total body weight; they don't keep up with intrauterine growth rates after they do start growing; and thus they end up growth restricted by term. A principal reason for this failure to achieve desired postnatal growth is inadequate nutrition, as evidenced by cumulative deficits in energy and protein [1]. While some recent observations indicate that with more optimal nutrition we are doing better [2], others indicate that at least half of these very preterm infants still demonstrate postnatal growth failure, much of which is severe [3, 4]. Even today we still are not achieving nutritional goals by the end of the first week of life, despite the critical developmental stage of these very preterm infants [5].

More optimal nutrition of very preterm infants rests on several basic principles [6, 7, 8]. Metabolic and thus nutritional requirements do not stop with birth, and the metabolic and nutrient requirements of the very preterm infant are equal to or greater than those of the fetus of the same gestational age. Thus the preterm infant should receive nutrients that at least match what the fetus of the same gestational age receives. Furthermore, the smaller the infant, the lower the amount of nutrient stores that are available for metabolic needs. As a result, parenteral (IV) nutrition is always indicated when metabolic and nutritional needs are not met by enteral feeding. IV nutrition should start right after birth to match the relatively continuous supply of nutrients that the fetus receives. Starting maternal or donor milk as soon after birth as possible and advancing enteral nutrition more quickly (20-30 ml/kg/day) have successfully maintained gestational age appropriate nutrient intakes and have allowed weaning off IV nutrition sooner, reducing adverse effects of hyperglycemia and central line associated bacterial systemic infection. Milk feedings reduce the incidence of NEC and prolonged milk and breastfeeding promote neurodevelopment. Early protein losses are minimized and positive nitrogen/protein balance is promoted by providing ~70-80 (IV) to ~90-110 (enteral) kcal/kg/d of total energy and 3-4 g/kg/d of amino acids. Protein is fundamental for growth, but it particularly improves growth of the brain and body lean mass. Growth of length is directly associated with better neurodevelopmental outcomes [9]. Excess protein, >4 g/kg/day, does not enhance and may harm development, and excess energy intake (>120 Kcal/kg/day) clearly leads to development of obesity [10].

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Caffeine from Delivery Room to Discharge and Beyond?

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Caffeine is an alkaloid that is naturally found in a variety of plants, such as tea and coffee and it belongs to a group of purine alkaloids called methylxanthines [1]. Methylxanthines stimulate the central nervous system, stimulate cardiac muscle, promote diuresis and relax smooth muscle [1]. Using caffeine as a therapeutic agent in neonatology became widespread after the results of the international Caffeine for Apnea of Prematurity (CAP) trial were published [2, 3]. CAP was launched to determine whether survival

without neurodevelopmental disability at a corrected age of 18 months is improved if apnoea of prematurity is managed without caffeine in infants at a high risk of apnoeic attacks [3]. The CAP trial showed that neonatal caffeine therapy reduces the risk of bronchopulmonary dysplasia and decreases the incidence of cerebral palsy and cognitive delay at 18 months [3, 4]. The median age of starting study medication in the CAP trial was 3 days and the median age of stopping caffeine was 34.4 weeks postmenstrual age (pma) [3]. Neonatologists now wonder whether caffeine started earlier than 3 days and given longer than 35 weeks pma further improves health outcomes.

Since then multiple studies have attempted to address the optimal timing of caffeine administration. A recent observational study from the Canadian Neonatal Network that analyzed 2108 preterm infants <29 weeks' gestation concluded that early (within 2 days of birth) caffeine therapy is associated with better neurodevelopmental outcomes compared with late caffeine therapy [5]. Based on this study and a systematic review that includes, amongst others, observational studies comparing early versus late caffeine therapy in preterm neonates [6], the European consensus guidelines on the management of respiratory distress syndrome recommend that "early caffeine should be considered for babies at high risk of needing mechanical ventilation such as those on non-invasive respiratory support". [7].

But what about the duration of caffeine treatment and extending caffeine treatment beyond 35 weeks pma? A recently published observational study evaluated the effect of duration of caffeine use on long-term neurodevelopmental outcomes at 3 years corrected age in preterm infants with birthweights ≤ 1250 g and concluded that the duration of caffeine use in premature infants does not impact on long-term outcomes at 3 years corrected age [8]. A randomized controlled trial (RCT) in which 98 preterm infants were assigned to either an extension of caffeine treatment or to usual care, showed that intermittent hypoxia can be reduced by extended caffeine treatment but no information on the clinically more relevant long-term neurodevelopmental outcome was provided [9]. Thus, until more information from well conducted RCTs becomes available, a reasonable suggestion may be to follow the instructions from the CAP trial in which the study drug was discontinued permanently at the discretion of the local clinicians. Furthermore, CAP recommended "to continue therapy with the study drug until the infant had tolerated at least five consecutive days without the use of positive airway pressure" [3].

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Pre- and Post-Natal Steroids: A Critical Appraisal

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Antenatal corticosteroids – current issues: A single course of antenatal corticosteroids in women at risk of preterm birth may accelerate fetal lung maturation and significantly reduce the incidence of RDS, IVH, NEC, late sepsis and mortality [1]. No clear effect has been demonstrated in randomized trials regarding BPD or neuro-developmental outcome although a recent cohort study did identify increased risk for behavioral or psychiatric problems in childhood [2]. In addition, long term follow-up at age 29-36 years in a Canadian cohort who had been exposed to corticosteroids in utero revealed increased risk for anxiety and depression [3]. Debate continues regarding the relative benefits and risks of repeated courses given to women at ongoing risk of preterm birth. A new individual participant data meta-analysis of single vs. multiple studies included 11 trials with 5,915 infants [4]. Multiple courses were associated with a modest reduction in need for respiratory support, but also potentially adverse effects on weight and blood pressure.

In an era of expanding indications for antenatal corticosteroid administration such as late prematurity, peri-viability and even elective cesarean section, we must weigh documented benefits against the potential for adverse effects. In this context, it is worth noting that very little information is available regarding the most appropriate dosing regimen for antenatal corticosteroids. Indeed, recent studies in sheep have shown that low dose betamethasone acetate is as effective as the routine, combined betamethasone phosphate-acetate preparation (Celestone) or dexamethasone in inducing fetal lung maturity, as measured by surfactant protein mRNAs and mechanical lung properties [5]. Further research may allow for individualized use of this powerful intervention.

Postnatal corticosteroids – enduring questions: Early postnatal systemic dexamethasone ameliorates BPD, while increasing risk for adverse neurodevelopmental outcome. Accordingly, their use is routinely limited to infants with moderate-severe BPD in whom the balance of effects appears more to be positive [6]. As an alternative, hydrocortisone has been studied recently in RCTs including the Premiloc trial that showed a modest benefit in survival without BPD and no significant effect on neurodevelopmental outcome [7]. The Stop-BPD trial failed to show similar short-term effects and follow-up is awaited, while a large NICHD trial is also

underway [8]. The combination of surfactant with budesonide has shown positive effects in two RCTs and a number of trials of this promising approach are underway [9]. Inhaled corticosteroids may also offer improvement in BPD although mixed results have been reported regarding mortality risk [10]. The search for a magic bullet to prevent the scourge of BPD races on.

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Stem Cells: The Magic Cure for BPD and Brain Damage?

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Advances in perinatal medicine have allowed the survival of remature infants at the limit of biological viability. As a consequence, prevention of the ever more immature lung and brain have become more challenging [1]. Next generation therapies that enable both, injury prevention/repair and proper organ development are required to substantially impact outcome of extreme prematurity. Stem cell-based therapies offer a new hope in preventing organ damage in extreme preterm infants [2]. Preclinical studies have demonstrated the lung and brain protective effects of exogenous administration of a variety of cell therapies in animal models of disease [3]. Mesenchymal stromal cells (MSCs), identified over 40 years ago in the bone marrow as niche cells crucial for the proper functioning of hematopoietic stem cells, have advanced to the forefront of cell-based therapies. Contrary to the initial hypothesis, cell engraftment and differentiation do not contribute to the repair mechanism. Instead, MSCs seem to orchestrate the repair process by cell-cell contact, modulate the immune response and release factors that promote lung and brain growth [4]. Early phase clinical trials, fuelled by these promising preclinical studies, have begun and indicate feasibility and absence of toxicity in a small number of extreme preterm infants [5]. While the enthusiasm in the neonatal community is palpable, major knowledge gaps remain. In parallel to well-designed early phase clinical trials based on robust rationale, laboratory research is needed to better understand the biology of MSCs and other putative repair cells, develop reliable potency assays that predict therapeutic efficacy, and enable the manufacturing of high quality, safe and efficient cell products. Maintaining the appropriate balance between discovery and evidence-based approach will be critical for cell therapies to fulfil their promise in substantially improving the outcome of extreme preterm infants without repeating past errors.

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Patent Ductus Arteriosus: Watch and Keep Cool?

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Patent ductus arteriosus (PDA) is one of the most frequent diagnoses made in very preterm neonates. Diagnosis and management of PDA remains controversial 40 years after the first randomized clinical comparing prophylactic surgical ligation versus medical management of a moderate to large PDA in preterm infants <29 weeks' gestational age (GA). [1] Major changes have happened since this study including increase in the use of antenatal steroids, surfactant therapy for respiratory distress syndrome, routine use of echocardiography to diagnose PDA and changing patient population characteristics, like, the extremely low birth weight (ELBW) infants with PDA. Prolonged patency of PDA has been shown to be associated with many morbidities, like, bronchopulmonary

dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and increase in mortality in preterm infants. [2] However, recent studies have shown no increase in morbidities, like, BPD, ROP, NEC or death. [3] Medical care of ELBW infants has also evolved over time with fluid restriction, diuretics and early pharmacological treatment of "symptomatic" PDA. Diagnosis of PDA is often made based on clinical signs and symptoms, like, active precordium, bounding pulses, heart murmur, wide pulse pressure, evidence of pulmonary over-circulation, hypotension needing inotropes, and low urine output. Typical echocardiographic criteria for a hemodynamically significant PDA (hsPDA) include ductal diameter >1.5 mm, low left ventricular output (<200 ml/kg/min), diastolic flow reversal in the descending aorta, absent or reverse diastolic flow in either superior mesenteric artery or middle cerebral artery, and myocardial dysfunction. Pocket echocardiography systems (PES) are available to make the diagnosis of PDA in many centers. Bedside near infrared spectroscopy (NIRS) monitoring has also been used to diagnose hsPDA in preterm infants. [4] Despite the improvements in perinatal care practices, several RCTs with pharmacologic closure of PDA have shown no short- or long-term benefits when compared with "watch and wait" approach. Other issues are lack of consensus on what constitutes a hsPDA and estimating shunts or effects of PDA on cardiac or lung function and on systemic circulation, more specifically, on cerebral circulation. Surgical treatment is associated with poor neurodevelopmental outcomes when compared to medically managed PDA. In spite of the many controversies surrounding PDA management, newer minimally invasive surgical techniques, like, trans-catheter closure of PDA has been approved by FDA for use in preterm infants >700 g with a postnatal age ≥3 days. [5]

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