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Women Are Designed to Deliver Vaginally and Not by Cesarean Section: An Obstetrician's View

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Worldwide, there is a rapid increase in deliveries by cesarean section. The large differences among countries, from about 16 to more than 60%, suggest that the cesarean delivery (CD) rate has little to do with evidence-based medicine. In this review, the background for the increasing CD rate is discussed, as well as the limited positive effects on neonatal outcome, in both term and preterm neonates. Negative effects of CD, including direct maternal morbidity, complicated subsequent pregnancies and iatrogenic early delivery resulting in increased neonatal morbidity, are discussed in addition to long-term implications for the offspring involving altered development of the immune system. The 'battle' to lower the CD rate will be difficult, but we should not forget that women are designed to deliver vaginally and not by cesarean section.

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Stabilization of Very Immature Preterm Infants in the Delivery Room: Pitfalls and Promising Strategies

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In 2003, at the Royal Women's Hospital in Melbourne, we started investigating neonatal resuscitation by recording videos and signals of inspiratory and expiratory gas flow, tidal volumes, mask or endotracheal gas leak, inflation pressures and times, spontaneous breathing patterns, oxygen saturation (SpO_2), heart rate and expired carbon dioxide [1, 2]. We realised there were aspects that we could not investigate in babies and so worked with the Prof. Hooper at Monash University, Melbourne, studying fetal and neonatal lambs and rabbits [3, 4]. We realised full resuscitation is very rare in babies and what we do is help them transition from in utero to ex utero breathing. We suggest it is more appropriate to call this stabilisation [5]. **What We Learned:** Intermittent counting of heart rate is inaccurate. Dynamic, heart rate and SpO_2 changes can be obtained by about 90 s after birth with an oximeter probe applied to the right wrist [6]. Seeing changes in heart rate rather than heart rate every 30 s is the best early guide to the success of any resuscitation. At 1 min, a heart rate <100/min occurs in about half of healthy babies and so is not a good indication of asphyxia, as long as the baby has good tone [7]. Most bradycardia and hypotension, immediately after birth, is due to vagal stimulation, probably due to clamping of the umbilical cord too early after birth [8].

There is no evidence for using 30 or 60 s after birth to decide when to start ventilation. Most people take longer than this just assessing the baby [9]. Birth is a stressful time and babies often need longer to recover and start breathing. Facemask ventilation is difficult, with a large leak often being a serious problem even for experienced neonatologists [10]. Unfortunately, it is difficult to assess the degree of leak. There is no facemask that is leak free. It is how they are positioned and held on the face that is important. Mask hold and positioning techniques are best taught with a leak-free manikin and a respiratory monitor [11]. It has been suggested it does not matter if there is a mask leak because the resuscitators can see the effect of ventilation from chest rise and heart rate. Unfortunately, this is not accurate [12]. With a variable mask leak, it is likely that either inadequate tidal volume is delivered or is very large and potentially damaging. From recordings of mask ventilation, airway obstruction is common even though appropriate inflating pressure is used [13]. Causes of the obstruction have not been elucidated. The only way to know how much leak is occurring, whether there is airway obstruction and the amount of tidal volume delivered, is by using a flow sensor and display of flow and tidal volume [14]. It has been suggested that very preterm babies must be ventilated from birth because they do not breathe. However, the majority will start to breath or crying after birth [2]. They need help with continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) to aerate their lungs [15]. Inspired oxygen is toxic for neonates and should not be used unless really needed [16]. It is difficult to judge cyanosis accurately [1]. In all babies, SpO_2 is about 60% just after birth and can take about 10 min to reach the mid 90s. Graphs of the normal changes in SpO_2 after birth have been produced and should be used to help decide whether the fraction of inspired oxygen (FiO_2) should be changed [7, 17]. Probably, it is best to start with air and only increase FiO_2 if it is needed. The main reason a newly born baby has a low SpO_2 is that the lungs are unaerated and full of fluid. Before gas exchange can take place, this fluid needs to be cleared. In weak preterm or compromised infants, this is best aided with PEEP immediately after birth to assist the formation and maintenance of a functional residual capacity. Before oxygen is considered in apnoeic infants, lung aeration should be facilitated with PEEP and probably a prolonged inflation for at least 20 s with a peak inspiratory pressure of 30 cm H_2O. CPAP, PEEP and sustained inflations can only be given with a T-piece device. About 50% of very preterm infants can be managed with CPAP and do not need intubation and surfactant [18]. Despite guidelines suggesting neonatologists should judge the viability in very preterm infants immediately after birth to help decide on resuscitation, their judgment is imprecise [19]. It is not possible to pick the winners and losers by observation. There are times when, with apparently appropriate tidal volumes, a baby does not respond to ventilation. Measuring whether expired CO_2 is detected helps assess whether ventilation is occurring [20]. In summary, to improve and understand neonatal resuscitation it should be guided by monitoring and displaying relevant physiological signals.

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3

When and How to Give Surfactant?

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Authoritative committees in the United States and in Europe have proposed recommendations and guidelines regarding the management of the respiratory distress syndrome (RDS) [1, 2]. These guidelines include specific evidence-based recommenda-

tions regarding the use of surfactant, detailing which surfactant administration strategy, which surfactant product and which surfactant dosage might be optimal. In general, these guidelines reflect a clear evidence basis for the recommendations. However, as with all guidelines and recommendations, there are areas of controversy and there are areas of newly emerging research. **Surfactant Strategy:** Surfactant therapy, whether used in infants at risk of RDS (prophylaxis) or in infants with established RDS (rescue or selective treatment), is effective in reducing pneumothorax and mortality [3–6]. However, the preferred approach to treatment and the timing of treatment remains controversial. Clinical trials from the 1990s strongly supported the use of prophylactic surfactant and ongoing ventilator support in infants at high risk for RDS (typically defined as 30 weeks of gestation or less) as opposed to later treatment of these infants with worsening RDS. However, recent studies have suggested that in infants who have received a full course of antenatal steroids, stabilization on nasal continuous positive airway pressure (CPAP) immediately after delivery may be the superior approach [7]. If an infant is stabilized on CPAP, it is unclear whether that infant might benefit from surfactant therapy prior to developing frank signs and symptoms of respiratory insufficiency; likewise, it is unclear what the threshold for treatment should be. The European guidelines suggest that infants <26 weeks of gestation should receive surfactant treatment when the requirement for supplemental oxygen is >30%, and infants >26 weeks of gestation should receive surfactant when the requirement for supplemental oxygen is >40%. These seem reasonable cut points based on the available clinical data. In this situation, a variety of approaches to surfactant administration have been taken. The InSurE approach calls for intubation, intratracheal surfactant administration and rapid extubation to CPAP or nasal intermittent positive pressure ventilation immediately following surfactant administration [8]. Recent data have suggested that even less invasive approaches to surfactant treatment may be advantageous. Minimally invasive surfactant treatment using thin catheters and administering surfactant to spontaneously breathing infants on CPAP has been used in studies in Germany and Australia with promising early results [9, 10]. Despite our best efforts to support infants less invasively, many infants will have worsening RDS and need further support. In intubated infants with RDS, the consensus guidelines state that a policy of early rather than late rescue surfactant is the optimal approach. **Surfactant Products:** Current guidelines recommend the use of animal-derived surfactant preparations. Multiple studies comparing animal-derived surfactant preparations to non-protein-containing synthetics support this recommendation [11]. The use of animal-derived products is associated with a decrease in pneumothorax and a decrease in mortality. Emerging research is evaluating synthetic surfactant preparations that include peptides or whole protein that, when added in an aqueous dispersion of phospholipids, function in a fashion similar to endogenous pulmonary surfactant protein. Two clinical trials suggest that these products may be as effective as animal-derived surfactant preparations [12, 13]. It remains to be seen whether or not these products are superior or safer than the currently available animal-derived products. **Surfactant Dosage:** Evidence from animal models and clinical trials supports a minimum dose of 100 mg phospholipid/kg. In trials comparing 100 mg of poractant α or beractant to 200 mg of poractant α, the 200-mg dose appears to lead to an improved clinical outcome [14]. However, few trials have compared dosages of similar surfactant products. In either case, infants who are intubated and have signs and symptoms of RDS should be given surfactant as soon as possible and infants who have persistent or relapsing disease 12 h after dosing should be considered for repeat dosing [15, 16]. **Conclusions:** Research continues to optimize surfactant therapy, including the evaluation of less invasive surfactant administration and surfactant products containing synthetic proteins. It remains to be seen whether this research will lead to further improvements in our use of surfactant and clinical outcome in newborn infants.

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How Much Oxygen Is Tolerable in the Delivery Room?

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Shortly after oxygen was discovered as an element in the 1770s it was introduced in newborn care and resuscitation. When in 1861 and 1862 Little and Mitchell, respectively, described cerebral palsy as a consequence of birth asphyxia, oxygen was considered as a cornerstone in newborn resuscitation. In 1928, Flagg developed a device delivering pure oxygen with CO_2 during newborn resuscitation [1]. In spite of the fact that it was understood in the 1950s that oxygen may be detrimental to premature infants, the common belief was that the brief exposure of pure oxygen during resuscitation after birth had no negative impact on the newborn [2]. The introduction of the Apgar score contributed further to an uncritical use of oxygen for newborn resuscitation. Virginia Apgar [3] herself used oxygen liberally. Color is one of the variables in the Apgar score, in order to become pink the first minutes of life oxygen must be delivered. Therefore, in many centers it became common practice to 'pink up' newborn babies by giving them oxygen immediately after birth in order to achieve a high Apgar score. Today, we know this may be detrimental and the Apgar scoring has probably done considerable harm to the world's newborn infants since its introduction 60 years ago. In 1980, we for the first time questioned the practice of giving high oxygen concentrations during resuscitation. The rationale was our new understanding that excess free radicals may be generated during posthypoxic reoxygenation [4]. A number of animal studies and 10 clinical studies published from 1993 to 2007 showed that it is feasible to start resuscitation with air instead of 100% oxygen. Further, accumulating data strongly indicated that hyperoxic reoxygenation might even be harmful [5]. **Term Newborn Infants:** Several meta-analyses have demonstrated the beneficial effect of starting resuscitation of term or near-term infants with air instead of 100% oxygen. In the latest meta-analysis including 10 studies with more than 2,000 babies [6], the relative risk for neonatal mortality of 0.69 (95% CI 0.54–0.88) was in favor of air. Thus, international guidelines were changed recommending to start resuscitation of term and near-term newborns with air instead of 100% oxygen when needing positive pressure ventilation at birth. In 2010, the International Liaison Committee on Resuscitation recommended: 'In term infants receiving resuscitation at birth with positive pressure ventilation, it is best to begin with air rather than 100% oxygen' [7]. The 2012 WHO guidelines stated: 'In newly-born term or preterm (>32 weeks gestation) babies requiring positive-pressure ventilation, ventilation should be initiated with air' [8]. It has been estimated that the change in practice from pure oxygen to air may

save around 250,000 newborn lives annually. Air substituting pure oxygen opens up for resuscitation in many areas where oxygen was not available. A recent study showed that 30% of fresh stillbirths may be rescued by air ventilation at birth, translating to approximately 300,000 additionally saved lives annually [9]. Thus, more than half a million newborn lives may be saved each year by air resuscitation. In the immediate postnatal period, it seems important to keep oxygen tension within normal values. Recently, a study by Kapadia et al. [10] demonstrated a lower incidence of severe and moderate hypoxic ischemic encephalopathy and less need for hypothermia treatment in asphyxiated newborns transferred from the delivery room to the intensive care unit with a physiologic versus a high PaO_2. **Preterm Infants:** There has been uncertainty about how to oxygenate preterm infants ≤32 weeks needing ventilation after birth. A few smaller studies testing out for instance 30 versus 90 or 21 versus 100% oxygen have been published [11–13]. Escrig et al. [11] and Vento et al. [12] have demonstrated that starting with 90 instead of 30% oxygen increases oxidative stress and markers of inflammation for several days. A recent meta-analysis and systematic review of 10 studies including 676 babies compared outcome of babies started with low (0.21–0.30) or high inspired oxygen (FiO_2; 0.60–1.0). There was no significant difference in mortality although the relative risk was 0.62 in favor of low initial FiO_2 (95% CI 0.37–1.04) [14]. There were no differences regarding bronchopulmonary dysplasia or intraventricular hemorrhage. Based on these studies, it may be reasonable to start with a low FiO_2 in babies <33 weeks in line with WHO recommendations: 'For preterm babies born at or before 32 weeks gestation, it is preferable to start ventilation with 30% rather than 100% oxygen. If this is not possible, ventilation should be started with air' [8]. **Conclusion:** Term newborn infants in need of ventilation at birth should be started with air instead of 100% oxygen. Their PaO_2 should be kept at physiologic ranges after the resuscitation. Until further evidence, preterm infants <33 weeks could be started with a low FiO_2, between 21 and 30% oxygen. In both term and preterm babies, FiO_2 should preferably be adjusted during resuscitation to approach the normal development of saturation during the first 10 min of life [15].

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5

Sustained Inflations for Neonates in the Delivery Room – What Is the Evidence?

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Recommendations for neonatal resuscitation were often based on weak scientific evidence for many years [1]. Based on the current knowledge, the single most important key element of successful neonatal transition is probably adequate lung aeration immediately after birth [2]. Lung aeration is often impaired in preterm infants because of their poor respiratory effort and instability of their chest wall [3, 4]. Although chest compressions and/or use of medications are rarely needed during resuscitation, respiratory support may be required especially in preterm infants [5]. Recent studies suggest that less invasive techniques of respiratory support during resuscitation in the delivery room and during early life may help to avoid mechanical ventilation [6–9]. The use of prolonged (sustained) inflations (SI) to overcome the increased resistance, i.e. time constant in a fluid-filled lung, has been described by Vyas et al. [10] in 1981 as an effective method to aerate the lung in intubated asphyxiated term neonates. The noninvasive application of sustained lung inflations as part of a successful noninvasive delivery room management approach for very low birth weight infants was first reported by Lindner et al. [11]. In a series of nicely conducted animal studies, sustained inflations lasting up to 15 s were shown to aerate the lungs from the first inflation and were associated with a more uniform aeration [12–14]. Currently, only limited clinical data on the effects of SIs for resuscitation in preterm infants are available. Harling et

al. [15] randomly assigned preterm infants (n = 52) to a 2- versus a 5-second SI as the initial inflation and found no difference in proinflammatory pulmonary cytokines as the primary outcome. Lindner et al. [6] found no differences in death or respiratory outcomes comparing a strategy using 15-second SIs with regular intermittent positive pressure ventilation. The study was closed early due to low recruitment and therefore has only limited power to detect differences in relevant outcomes. However, there was a trend to a lower rate of subsequent failure of continuous positive airway pressure (CPAP) in the SI group. A strategy using SIs with 10-second duration at 20 cm H_2O pressure, use of nasal intermittent mandatory ventilation and CPAP as compared to bag and mask ventilation in the delivery room without subsequent use of noninvasive respiratory support reduced the rate of infants needing intubation and mechanical ventilation and the rate of bronchopulmonary dysplasia [7]. Since a bundle of interventions was tested in this study, it is difficult to judge the impact of SIs alone. Another study used a strategy using initial SIs with positive end-expiratory pressure/CPAP immediately after birth and found a reduced rate of intubation/mechanical ventilation and bronchopulmonary dysplasia in preterm infants as compared to historical controls using intermittent positive pressure ventilation/CPAP [16]. Another randomized controlled study on the effects of SIs on the need for mechanical ventilation has finished patient recruitment recently, but results of this study have not been published [17]. In theory, overdistension during SI may cause air leaks and may impair venous return and decrease cardiac output, as suggested by animal studies using large inflation pressures, i.e. tidal volumes for 5 s [18, 19]. In contrast, the increase in pulmonary blood flow at birth was not impeded and carotid blood flow did not change when an SI (40 cm H_2O for 1 min or until a tidal volume of 20 ml/kg was administered) was applied in preterm lambs at birth [14]. No relevant adverse effects using SIs, such as an increased rate of pulmonary air leaks, intraventricular hemorrhage or negative hemodynamic effects, were found in the randomized trials so far [6, 7, 16]. One study showed that very low birth weight infants supported using a standardized protocol including SIs increased their cerebral oxygen saturation at least as fast as full-term infants not requiring any respiratory support [20]. However, the limited evidence available based on the clinical trials mentioned above does not suggest that there may be an increased risk for these adverse outcomes. In summary, the use of SIs may be a useful mode of respiratory support to aerate the lung of preterm infants with poor respiratory effort and may help to improve noninvasive concepts of delivery room care. However, further studies are needed to assess the appropriate pressure and inflation duration, and to study the effects of different interfaces such as masks or prongs. Large randomized controlled trials are needed to prove efficacy and safety of SIs in different term and preterm populations before SIs can be generally recommended. A large, National Institute of Child Health and Human Development-sponsored trial assessing the effects of SIs on survival without bronchopulmonary dysplasia in 600 preterm infants with a gestational age of 23–26 weeks in the USA, Australia, The Netherlands, Italy and Germany is going to start patient recruitment very soon.

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6

Face Mask or Nasal Prong Immediately after Birth?

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Most preterm infants breathe spontaneously at birth [1]. A meta-analysis of large randomised trials demonstrated that supporting spontaneous breathing with continuous positive airway pressure (CPAP) at birth, in preference to routine intubation for surfactant administration and/or mechanical ventilation, leads to a reduction in mortality or chronic lung disease in preterm infants [2]. The majority of preterm newborns receive breathing support. This breathing support is given with manual ventilation devices most often via a face mask, but occasionally via a nasal prong (AKA nasal tube/nasopharyngeal tube), a shortened endotracheal tube inserted into the infant's nasopharynx. A single-centre retrospective cohort study showed that the introduction of a multifaceted intervention that included using a single nasal prong instead of a face mask more than halved the rate of intubation in the delivery room (DR) and was associated with reductions in the rates of intubation during hospitalisation and chronic lung disease [3]. A randomised study of a similar multifaceted intervention demonstrated >50% reduction in the rate of DR intubation, and reductions in the rates of intubation within 72 h and of moderate-to-severe bronchopulmonary dysplasia [4]. As the interface was only one of several differences in the respiratory support the groups received (others included the ventilation device used, use of positive end-expiratory pressure and timing of starting CPAP) in both of these studies, it is not possible to determine the relative contribution of the interface to the differences observed between the groups. The effect of using a nasal prong instead of a face mask was examined in two unblinded randomised trials, the MONT trial [5] and the DROPOM trial [6]. In both trials, very preterm infants were randomised before birth to receive respiratory support with a T-piece via a nasal prong or face mask. In the MONT trial, infants received 21% O_2 via either a 7-cm nasal prong or a Laerdal mask, while in the DROPOM trial they received 30% O_2 via a 5-cm prong or a Fisher and Paykel mask. Infants in MONT were intubated in the DR if they remained apnoeic and bradycardic despite positive pressure ventilation, if they received chest compressions or if they had oxygen saturation (SpO_2) <85% despite CPAP of 8 cm H_2O in 40% O_2. In DROPOM, infants were intubated in the DR if they had apnoea and/or bradycardia despite positive pressure ventilation. MONT infants who were stabilised on CPAP were all transferred to the neonatal intensive care unit on CPAP via a nasal prong, whereas infants in DROPOM stabilised on CPAP were transferred to the neonatal intensive care unit on their allocated interface. The primary outcome of the MONT trial was intubation for pre-determined failure criteria within 24 h of birth (one or more SpO_2 <88% despite CPAP 8 cm H_2O in >40% O_2, apnoea despite caffeine or respiratory acidosis on blood gas). The primary outcome of the DROPOM trial was intubation in the DR; the decision to intubate thereafter was at the discretion of the treating clinician. MONT planned to enrol 648 infants in an attempt to show a 20% reduction (from 55 to 44%) in the rate of intubation within 24 h with nasal prong. DROPOM planned to enrol 142 infants to attempt to show a 40% reduction (from 62 to 37%) in the rate of DR intubation with

nasal prong. Enrolment to MONT was stopped after interim analysis showed that the chances of finding a difference in the primary outcome between the groups was remote. A total of 363 infants (mean gestational age 27 weeks and body weight 1,012 g) were enrolled. There were no differences between the groups in the rate of intubation <24 h (prong 54% vs. mask 55%) or in the DR (23 vs. 31%), or in important secondary outcomes between the groups. A total of 144 infants (mean gestational age 28 weeks and body weight 1,117 g) were enrolled in the DROPOM trial. There were no differences in the rates of intubation in the DR (prong 15% vs. mask 15%) or <72 h (67 vs. 63%), or in important secondary outcomes between the groups. Neither study demonstrated a difference in DR intubation. In the DROPOM trial, though there was no difference between the groups, there was a dramatic reduction in the rate of DR intubation overall. The rate of intubation in DROPOM outside the DR should be interpreted with caution as the indication for intubation was not standardised. While the studies may not be large enough to exclude small differences in the rate of outcomes between the groups, these differences would be of a magnitude that would be of dubious clinical importance. Face mask and nasal prong appear to be equally effective and safe interfaces for supporting preterm newborns; the choice should be determined by preferences of the carers.

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7

Delayed Cord Clamping for All Neonates?

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Although the clamping of the umbilical cord appears as a simple procedure, its timing and the way it is performed have significant effects. Its influence on the neonatal period as well as infancy and later development is frequently underestimated. Furthermore, the impact needs to be taken in perspective: there are approximately 350 births per minute in the world in which the procedure is necessarily performed [1]. The description by Erasmus Darwin [2] of this practice in 1801 resembles a hot topic of discussion nowadays: he then recommended 'tying and cutting' the umbilical cord 'only after pulsation ceased and the child has repeatedly breathed' [1]. It has been known for a long time that delaying cord clamping (DCC) allows the flow of blood from the placenta to the infant, known as placental transfusion. The volume of this transfusion has been estimated by measuring residual volume at the placenta, by the increment in weight of the infant after birth and even by performing actual measurements of the infants' blood volume [3–5]. It can be estimated that when the cord is clamped immediately after birth, 33% of the infants' blood volume will remain at the placenta, but if the cord is left unclamped to the end of placental transfusion, the residual volume would result in only 13% [5]. Gravity and the onset of respiration may also influence the volume of transfusion and have been the matter of investigation and controversy [3, 6]. A recent Cochrane review evaluated 15 randomized controlled trials comparing early (before 60 s) versus delayed cord clamping in term newborns involving 3,911 maternal infant dyads [7]. They found with DCC a weight increment (mean 101 g, 95% CI 45–157 g) representing a placental transfusion of approximately 96 ml. They also found higher hemoglobin levels in the neonatal period and increased iron stores at 3–6 months of age in infants with DCC. Only one of the studies reported a marginal increase in infants requiring phototherapy in the DCC group. This review did not confirm any maternal complication (such as the previously reported increased frequency of postpartum hemorrhage). It is concluded that DCC should be recommended for term newborns in all places with available phototherapy. Several professional organizations currently recommend DCC [8, 9]. However, the compliance with the recommendation appears low [10]. Some obstetricians may still fear about postpartum hemorrhage, and in other cases cord blood banking may prompt an earlier clamping of the cord. However, a major issue which may relate with this low compliance is the suggested effect of gravity on the volume of placental transfusion and the proposal of holding the infant during the period the cord is unclamped at the level of the vagina or even lower. To hold a crying and slippery infant in this way for 2 min or even longer is uncomfortable, unnatural and delays the possibility of immediate contact with the mother [11]. The potential decrease in the volume of placental transfusion for infants held above the level of the placenta is mostly based on the study by Yao and Lind [3], where infants were placed at different vertical levels above and below the placenta and various timings of clamping the umbilical cord were performed. By measuring placental residual volume they concluded that gravity has a significant influence. However, that evidence was not obtained in conditions similar to those of the real scenario of vaginal deliveries. In the study by Ceriani Cernadas et al. [12], infants were held above the level of the placenta, on their mother's arms in vaginal deliveries and on their laps during DCC, and an increment in hemoglobin was still demonstrated. A Cochrane review concluded that there is insufficient evidence on the influence of gravity [13]. We recently reported a randomized controlled trial in normal term infants born by vaginal delivery [14]. In all cases, we obtained the infants' initial weight immediately after birth; 197 infants were held at the level of the vagina and 194 on their mothers' abdomen or chest, and in all cases the cord was clamped and cut at 2 min, and a second weight measurement was performed. The average weight gain was 55 g, with no differences between groups, even in the subgroup of infants whose mothers adopted a semi-sitting position. We concluded that gravity does not influence the volume of placen-

tal transfusion. We expect our study to help increasing the compliance with the recommendation of DCC in term infants born by vaginal delivery, which may result in a decreased risk of iron deficiency in infancy, a serious public health problem all over the world, and at the same time enhance maternal-infant bonding by allowing mothers contact with their infant immediately after birth. In premature infants, several studies and meta-analyses suggested some positive effects of DCC: stabilization of blood pressure and circulation, decreased need for blood transfusions, and lower incidences of intraventricular hemorrhage and necrotizing enterocolitis [15]. Recent studies in lambs have suggested that when resuscitation is needed, a smoother cardiovascular transition is obtained when ventilation is initiated without clamping the umbilical cord [16]. There are ongoing studies evaluating this possibility. In conclusion, DCC is an important maneuver showing many short- and long-term benefits in vigorous term and preterm infants, but with potential advantages even in infants needing resuscitation.

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8

Nasal Continuous Positive Airway Pressure or High-Flow Nasal Cannula?

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Nasal continuous positive airway pressure (NCPAP) is provided using a water column (bubble CPAP), a flow generator (infant flow driver) or a conventional ventilator. The user controls the pressure generated by varying the resistance to expiratory flow. Bubble CPAP systems use a constant gas flow rate that is set by the user, and the CPAP generated is assumed to be equal to the length of expiratory tubing that is immersed under water. Even during bubble CPAP, increasing the flow rate will result in an increase in intra-prong pressures at the level of the patient's nasal interface [1]. Tubing submersion depth during bubble CPAP is highly inaccurate, and care providers should instead rely on intra-prong pressure measurements. A major problem with the use of nasal prongs is the risk of nasal injuries, such as columellar necrosis and nasal deformities [2–5]. Furthermore, nasal mucosal injury acts as a site of entry for bacteria, resulting in nosocomial sepsis in preterm neonates [6]. Heated, high-flow nasal cannula (HHFNC) systems are increasingly being used due their ease of use. Because of high flows, they do generate substantial CPAP at the upper airways of infants [7–10]. One of the major limitations is that the pressure delivered is unpredictable and depends on the flow rates used, length and internal diameter of the nasal cannula, and the amount of leak at the nostrils. Nasal cannulas (0.2 and 0.3 cm in outer diameter) could generate up to 9.8 cm H_2O at flow rates of 2 l/min [10]. This positive distending pressure effect was felt to improve both oxygenation and thoracoabdominal synchrony. Serious complications, such as scalp emphysema, pneumo-orbitis and pneumocephalus, have been reported with use of HHFNC [11]. To decrease the delivered pressure during HHFNC, manufacturers have decreased the inner diameter of the nasal cannula or use a uninasal cannula. Nasopharyngeal washout of the dead space, better humidification and high bulk flow to match the inspiratory flow demands in patients who are tachypneic are some of the potential effects during HHFNC. However, higher humidification at the nasopharyngeal level does not translate into better humidification at the lower airways given the open-circuit design. Since pressures generated are neither measured nor controlled by the user, flow rates >2 l/min should not be used in preterm neonates. HHFNC systems are expensive compared to bubble CPAP systems. Preterm infants needing respiratory support should be stabilized with NCPAP. Since NCPAP failures leading to intubation are very high in infants with extremely low birth weight [12, 13], clinicians should consider starting nasal intermittent positive pressure ventilation as soon as possible in these infants, followed by weaning from NCPAP and subsequent use of a low-flow nasal cannula (<2 l/min). Additional studies are needed to evaluate the safety and efficacy of using HHFNC before it can be recommended for use in preterm neonates. The costs of HHFNC systems over bubble CPAP have to be taken into consideration given the lack of evidence for equivalency or superiority in resource-limited parts of the world.

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9

Should We Be Supporting Very Low Birth Weight Infants with High-Flow Nasal Cannulae or Continuous Positive Airway Pressure – Favoring High-Flow Cannulae

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This paper describes the use of non-invasive continuous distending pressure (CDP) as respiratory support for preterm infants. Continuous positive airway pressure (CPAP) and heated and humidified high-flow nasal cannulae (HFNC) are particularly discussed. The application of CDP has become the mainstay of respiratory management of neonates with respiratory distress [1]. Attributed effects are splinting of the upper and lower airways, increases in pulmonary gas volume and functional residual capacity, improvement in gas exchange and oxygenation, stabilization of spontaneous respiration and reduction in apnoea [2, 3]. Concerning our current understanding of CPAP, it is a widely held belief that CPAP is a stringent, pressure-controlled modality. However, investigations in the effect of mouth opening and leak under CPAP have clearly demonstrated that the measured tidal volume is significantly reduced with mouth opening and leak flow easily exceeds 20% of bias flow [4]. Since Gregory [5] introduced CDP pressure into neonatal care as head box CPAP in 1971 the application of CDP has evolved over single nasal prong to binasal prong CPAP [6]. A plethora of different CPAP devices is now available. Apart from technical differences, there is wide inter-institutional variation in CPAP practice, for instance the optimal CPAP level remains a matter of debate: for example a starting CPAP from 3 to 10 cm H_2O is being used in Germany [7]. Irrespective of the universal use of this treatment, nasal CPAP is prone to significant unwanted effects, such as cranial deformities, pressure sores, nasal erythema and necrosis, abdominal symptoms, pneumothorax and potentially sepsis [8]. Nasal cannulae have long been used to deliver oxygen to infants with chronic respiratory compromise and/or hypoxaemia [9]. A flow rate >1 l/min is regarded as 'high flow' [10]. Flows of non-heated, dry gas of 0.5–2 l/min were found to exsiccate the nasal mucosa and increase airway resistance. Humidification of medical gas without sufficient heating causes condensation and droplet aspiration. Recent technical improvements have evolved in small HFNC, which provide flows of up to 40 l/min of sufficiently heated and humidified gas. HFNC works via nasal prong interfaces like most CPAP devices, but the two systems differ significantly in their mode of action. Nasal CDP is generated within the CPAP device where the resistance is provided by the expiratory valve or water lock. In HFNC, CDP is developed within the nose or oro-pharynx as a result of the flow through the cannula combined with the infant's spontaneous respiration. Conversely, the resistance is determined by the leak between the nares and the cannula [11]. Different to nasal CPAP where physiological and clinical properties have been studied over decades, until recently, laboratory and clinical data on HFNC have remained scant [12]. HFNC has incorrectly been touted as 'poor man's CPAP' and was criticized as unscientific. New scientific evidence from bench-top and clinical studies has helped to understand HFNC mechanisms of action [11, 13]. It is understood that HFNC flush the nasopharyngeal dead space thereby allowing for more effective alveolar ventilation and oxygenation, provide sufficient flow to help reduce inspiratory work of breathing and reduce metabolic expenditure [14]. The efficacy of HFNC has now been investigated in over 20 controlled clinical trials. However, particularly some of the earlier trials were limited by insufficient power and/or poor methodology [15]. Recent large, prospective randomized controlled trials have compared HFNC to CPAP (3 trials) or nasal intermittent positive pressure ventilation (1 trial) as post-extubation treatment. Together, they include over 800 neonates. Results of these trials show that HFNC was as safe to use and not inferior to CPAP or nasal intermittent positive pressure ventilation [16–19]. Two studies found less nasal trauma in the HFNC groups. Klingenberg et al. [20] investigated patient comfort under CPAP and HFNC. They found no significant difference in comfort scores, but improved parental satisfaction in the HFNC group. Large, multicentre trials to investigate the use of HFNC as primary treatment for the respiratory distress syndrome are currently

under way. To summarize, HFNC have been shown to be efficacious and safe in very low birth weight infants after extubation, whereas the use of HFNC as a primary therapy for the respiratory distress syndrome requires further study. HFNC evolves as an easy-to-use alternative to nasal CPAP for certain clinical scenarios. It has lesser side effects and achieves higher nursing and parental contentment. Future trials should investigate for which type of infant and clinical condition HFNC proves to be most beneficial.

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Practical Issues of Targeting Oxygen in the Neonatal Unit

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Background: There is wide variation in practice regarding oxygen targeting for preterm infants. Trials in the 1950s, before targeting was possible, linked unrestricted oxygen to retinopathy of prematurity. The subsequent oxygen restriction increased mortality [1]. Blood gas analysers and transcutaneous PO_2 monitoring permitted targeting but the optimal PO_2 target range was never determined. Guidelines recommended a range of 50–80 mm Hg [2]. Pulse oximeter saturation (SpO_2) monitoring became the norm but it was introduced with little investigation. No trials were performed to show that it would improve outcomes in comparison with PO_2 monitoring and none were done to determine the optimal SpO_2 range. A SpO_2 range of 85–95% was considered acceptable [2]. PO_2 and SpO_2 are not linearly related and it is important to note that the 95% confidence intervals of PO_2 for the SpO_2 range 85–95% in oxygen-dependent preterm infants are around 28–67 mm Hg (3.8–8.9 kPa) [3], so the introduction of SpO_2 monitoring was associated with a substantial unresearched shift downwards in targeted PO_2 levels from previous recommendations. **Recent Evidence:** Five similar trials of SpO_2 targeting for preterm infants have now been published [4–8]. Three trials have reported follow-up outcomes [5, 7, 8] and 2 have reported outcomes to hospital discharge [6], with follow-up outcomes anticipated shortly. The evidence has been summarised in a meta-analysis by Saugstad and Aune [9]. **Mortality and Morbidity:** Data from 4,884 infants in the 5 trials show that the lower SpO_2 target range was associated with increased mortality [19.3 vs. 16.2%, relative risk (RR) = 1.18 (1.04–1.34)]. The point estimates for mortality from 4 of the 5 trials favoured higher SpO_2. The exception was BOOST (Benefits of Oxygen Saturation Targeting) II New Zealand which contributed 340 of the 4,884 infants. The 95% confidence intervals of the RR for mortality from the New Zealand trial (0.51–1.51) include those of the overall meta-analysis. The data from these trials probably underestimate the mortality risk of the lower SpO_2 range. Mid-way through the trials a problem with the oximeter calibration was identified [10]. This was corrected in 3 of the trials, allowing more effective targeting, and meta-analysis of the outcomes of the 1,725 infants treated with the revised oximeters showed an RR for mortality with lower versus higher SpO_2 targets of 1.41 (1.14–1.74) [10]. Mortality was 21.1% in the low target group and 15.3% in the high target group. The revised oximeters are similar to other oximeters in widespread use [10] and this may be the more generalis-

able mortality risk estimate. Hazard plots from the trials show that the difference in mortality arose gradually over many weeks. Necrotising enterocolitis affected 11.2% of infants in the low target group and 9.0% of infants in the high target group, RR 1.25 (1.05–1.49). Severe retinopathy of prematurity affected 10.7% of the low target group and 14.5% of the high target group, RR 0.74 (0.59–0.92). There was no significant difference between groups in any other reported short-term morbidity. **Disability:** Three of the trials have reported outcomes to 18 or 24 months [5, 7, 8]. There is so far no evidence that disability is increased in either randomisation group. Blindness is rare in both groups. The remaining data will be reported in 2014. **Future Practice:** These trials show conclusively that the intended SpO_2 target range influences mortality and morbidity. Further studies will be required, but the present evidence should influence practice. The mortality risk of lower SpO_2 targets outweighs any other adverse outcome. Retinopathy of prematurity is a serious condition but it can usually be treated and, although it is associated with adverse neurodevelopmental outcome, the same is true of necrotising enterocolitis. **Achieved versus Intended SpO_2:** The trial results are probably attributable to the achieved SpO_2 patterns. In the BOOST II UK and Australia trials, histograms of the percentage of time that infants spent at each SpO_2 value showed that in both study groups, the achieved SpO_2 values were higher than intended. The high target group had the peak of their distribution at 94%. The low target group had their peak at 90%. It was a distribution of achieved SpO_2 centred around 90% that was associated with increased mortality in the low target group. The other trials have not published detailed information about their achieved SpO_2 but the available information suggests that achieved SpO_2 in their low target groups was also higher than intended. The trial results may therefore be underestimating the risks of maintaining SpO_2 at values below 90%. Many infants are difficult to target and it is impossible to keep them within a narrow range at all times. Units vary in their success in achieving intended SpO_2 targets [11]. A greater focus on ensuring that oximeter alarm limits are set and adhered to will be necessary [12]. Compliance is better when alarm limits are set to the intended range rather than being wider [11]. Compliance is better when nurse staffing ratios are higher [13]. Staffing is important because the outcomes in the trials were determined over many weeks and not just the early days after birth. Servo-control systems are becoming available [14]. These appear to be more effective than manual control in delivering intended SpO_2 and will be capable of influencing clinical outcome. Because they are likely to result in a lower SpO_2 distribution than would be observed with routine nurse control, servo systems could worsen rather than improve outcome if they are not researched carefully to identify the control settings required to optimise outcomes. More than ever before there is evidence that oxygen saturation targets influence outcome. Every neonatal unit should have a clear policy on targeting and should audit their achieved saturation patterns.

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Is Nasal Ventilation a Good Alternative for Invasive Intermittent Positive Pressure Ventilation?

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The management of respiratory failure with invasive intermittent positive pressure ventilation (IPPV) has been one of the key factors responsible for improving survival of extremely premature infants. Though lifesaving, invasive IPPV is associated with a significant risk of acute lung injury and long-term pulmonary morbidity. For these reasons, there has been a concerted effort to explore less invasive alternatives to maintain gas exchange while minimizing complications associated with invasive IPPV in these infants. Two alternatives of nasal support, nasal continuous positive airway pressure (NCPAP) and nasal IPPV (NIPPV), have been

studied extensively in the last 3 decades, with varying success. Both NCPAP and NIPPV can stabilize lung volume resulting in improved gas exchange, less apnea and reduced upper airway obstruction and thoracoabdominal asynchrony. As initial respiratory support strategy, NCPAP has been studied in several large randomized controlled trials, all of which showed similar incidence of bronchopulmonary dysplasia (BPD) with use of CPAP when compared to invasive mechanical ventilation [1, 2]. A recent meta-analysis of these studies showed a modest decrease in the rates of BPD or death at 36 weeks postmenstrual age with early use of CPAP rather than intubation and mechanical ventilation [3]. However, these studies included relatively mature infants with a high antenatal steroid use, but still a large proportion of the infants in the CPAP groups required mechanical ventilation and surfactant administration during the first days after birth. Because of the high prevalence of failure with NCPAP, especially in smaller and sicker infants, there has been a resurgence of NIPPV use in preterm infants as an alternative for invasive support. Used as an initial strategy for the respiratory distress syndrome, NIPPV has had mixed results with some small studies showing significant benefit and reduction for the need of invasive ventilation [4]. However, the largest multicenter randomized controlled trial comparing NCPAP with NIPPV for both treatment of the respiratory distress syndrome and respiratory support after extubation failed to show any significant decrease in the incidence of BPD or death with NIPPV use [5]. Some of the reasons for the inconsistent results between different trials could be differences in patient populations with different background risk of BPD, and the variability in the settings and equipment used in different studies. In contrast, NIPPV has consistently been shown to be superior to NCPAP for the prevention of extubation failure. Some of these studies have also shown trends towards decreased rates of BPD in the NIPPV group compared to NCPAP [6]. One of the possible mechanisms why NIPPV is superior to CPAP is the higher mean airway pressure achieved during NIPPV. Synchronization of NIPPV cycles with the patient's inspiration can increase the transpulmonary pressure, which may be an additional mechanism to explain the improved outcomes with NIPPV. Though there have been some physiological studies showing decreased work of breathing with synchronized NIPPV as compared to NIPPV [7], there has been no randomized controlled study comparing the two modalities with respect to BPD or other long-term respiratory outcomes. One of the newer methods available for synchronization is neurally adjusted ventilator assist, which uses the electrical activity of the diaphragm to detect spontaneous inspiration and delivers positive pressure in proportion to the electrical signal from the diaphragm [8]. There are some short-term studies in small groups of preterm infants suggesting that this modality improves patient-ventilator interaction and reduces respiratory effort, but there are no long-term outcome data in this population. In conclusion, though nasal ventilation is used very commonly and has shown some short-term physiological advantages over NCPAP, evidence for long-term benefits in respiratory outcomes is not consistent. Furthermore, there are still many unanswered questions such as what NIPPV settings to use, the potential advantage of synchronization and the best way to achieve synchronization. Importantly, there is no evidence that NIPPV use is associated with an increased risk of adverse effects. Nasal ventilation is a viable alternative to invasive IPPV for many of the preterm infants, both as initial respiratory strategy as well as an adjunct to decrease extubation failure. Still, a large pro-

portion of the smaller and more immature infants are likely to fail and require invasive IPPV. It is important for clinicians to identify these infants early in their respiratory course to avoid complications associated with inadequate respiratory support.

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Bronchopulmonary Dysplasia: Past, Present and Future

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It is now approximately 50 years since the introduction of assisted ventilation to manage infants with the respiratory distress syndrome (RDS), formerly called hyaline membrane disease. Shortly afterwards, in 1967, the first description of bronchopulmonary dysplasia (BPD) was published [1]. Initial reports suggested that BPD was the result of exposure to very high oxygen concentrations administered by assisted ventilation [1, 2]. In 1975, I proposed that BPD was related not only to exposure of the immature lung to increased oxygen concentrations, but also to positive pressure ventilation administered over an extended period of time [3]. More recently, I (and others) suggested that it was most likely part of a continuum of pathology that includes the Wilson-Mikity syndrome [4–6] and might be better called chronic lung disease of prematurity [5, 6]. During the 1970s and 1980s, neonatologists dealt with a disorder that could be quite devastating, requiring weeks to months of assisted ventilation. This resulted in prolonged hospital stays and only gradual improvement in pulmonary function, or death from either cor pulmonale or severe fibrosis. The majority of infants who survived had been born with a gestational age of 28

weeks or more. After the initial report in 1980 of the successful administration of exogenous surfactant to treat RDS [7], extensive studies of surfactant were performed around the world and surfactants for use in RDS were approved by the Food and Drug Administration of the USA starting in 1990. Over the ensuing decade, many more extremely preterm infants survived, some with chronic lung disease. The infants who formerly had developed BPD (>27 weeks gestation) were now spared chronic lung disease, but the less mature infants developed what Jobe described as 'new BPD' [8]. In contrast to airway injury with alternating areas of overinflation and fibrosis of the lung parenchyma, 'new BPD' was characterized by arrested pulmonary development. Currently, a diagnosis of BPD is based largely on continued oxygen requirement at 36 weeks postmenstrual age, rather than on radiographic features of macrocystic and hyperinflated lungs. However, BPD may be overdiagnosed in some centers, because the use of oxygen saturation monitors has resulted in overuse of oxygen to maintain 'good' oxygen saturation [9]. Among the many preventive and therapeutic strategies for RDS (and consequently for BPD) that are currently available, antenatal corticosteroids and exogenous surfactant have proved to be the most efficacious [2, 10, 11]. This is particularly true for those whose gestational age is >27 weeks. However, caffeine and to some extend vitamin A may have a place in the management of BPD [12]. The role of postnatal corticosteroids remains debatable. At the present time, increasing emphasis is placed on the early use of continuous positive airway pressure (CPAP) as a preventive strategy. This approach was proposed in the 1980s [13], but more recent studies provide increasing evidence that early noninvasive CPAP (rather than proceeding directly to endotracheal intubation) may result in a decrease in the incidence of BPD [14, 15]. It seems likely that avoidance of endotracheal intubation and using minimally invasive surfactant techniques will be the approach in the future to prevent BPD [16, 17]. One recent study demonstrated a marked decrease in the incidence of BPD when surfactant was given by thin catheter during spontaneous breathing rather than using the InSurE technique (intubation, surfactant and extubation). In neonates with gestational age <28 weeks, BPD incidence was reported to be 13.6 versus 26.2%, respectively [18]. For those at risk for or who develop BPD, the possibility of using stem cells to prevent and/or treat BPD has been proposed. Bone marrow-derived mesenchymal stem cells (MSCs) have attracted the most attention and may prevent impaired alveolar and lung vascular development in oxygen-induced lung injury [19]. They may also attenuate lung inflammation and fibrosis [19]. MSCs have also been derived from human cord blood and shown to preserve both alveolar and lung vascular growth as well as lung function and to prevent pulmonary hypertension in rodents exposed to hyperoxia [19]. Additionally, after 2 weeks of oxygen exposure, airway delivery of MSCs restored alveolar growth and lung function in rats. Amniotic fluid stem cells may have similar effects to MSCs [19]. Whether or not such promotion of both lung repair and lung growth can be achieved in human newborn infants remains to be seen.

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Mesenchymal Stem Cells in Preterm Infants: The Magic Cure of Bronchopulmonary Dysplasia?

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Bronchopulmonary dysplasia (BPD) is a chronic lung disease which follows ventilator and oxygen therapy in very preterm infants [1]. Although the number of very premature infants at a high

risk for developing BPD is increasing because of advances in neonatal intensive care [2], BPD remains a major cause of mortality and lifelong morbidity without any effective ways of prevention or treatment having been developed yet [3]. Several recent studies have shown that mesenchymal stem cells (MSCs) attenuate hyperoxia-induced neonatal lung injury which simulates BPD in human infants, such as impaired alveolarization, increased inflammation, increased apoptosis and fibrosis [4–8]. Human umbilical cord blood (hUCB) is considered a better source of MSCs than other potential sources, such as bone marrow or adipose tissue, because of their ready availability and greater proliferative capacity and less antigenicity [9]. We have performed several preclinical studies regarding optimal route [4], dose [7] and timing [8] of hUCB-derived MSC transplantation in a neonatal hyperoxic lung injury model in rat pups. The benefits of MSC transplantation are primarily mediated by a paracrine rather than a regenerative mechanism [4, 6], and vascular endothelial growth factor secreted by transplanted MSCs is at least one of the critical paracrine factors that play seminal roles in attenuating hyperoxic lung injuries in neonatal rats [10]. We have also shown that the protection of MSCs against neonatal hyperoxic lung injury was persistent, and that no long-term toxicities, adverse effects or tumorigenicity were present 70 days after transplantation [11]. For the successful clinical translation of transplantation of hUCB-derived MSCS for an effective treatment of BPD, various preclinical toxicity and safety tests were done using hUCB-derived MSCs, which were produced with good manufacturing practices and tested with karyotype stability at up to passage 11 [4, 12]. Finally, we performed a phase I dose-escalating clinical study on the safety and feasibility of transplantation of hUCB-derived MSCs in preterm infants at high risk for developing BPD [12]. Intratracheal MSC transplantation was performed 10.4 ± 2.6 days after birth in 9 premature infants with gestational ages of 25.3 ± 0.9 weeks and birth weights of 793 ± 127 g. The first 3 patients were given a low dose (1×10^7 cells/kg) of cells; the next 6 patients were given a high dose (2×10^7 cells/kg). We compared the adverse outcomes including BPD severity in them with those in historical nested case-matched controls. The treatments were well tolerated, and no patients experienced serious adverse effects or dose-limiting toxicities attributable to the transplantation. When compared to the matched controls, BPD severity was lower and the other adverse outcome rates were not different in transplant recipients. Taken together, intratracheal transplantation of allogeneic hUCB-derived MSCs in preterm infants is safe and feasible, and warrants larger and controlled phase II as well as long-term follow-up studies.

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Patent Ductus Arteriosus: Increased Risk of Bronchopulmonary Dysplasia?

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The increased pulmonary blood flow resulting from left to right ductal shunting can negatively impact lung development and function and delay recovery from the respiratory distress syndrome [1, 2]. Infants with a symptomatic patent ductus arteriosus (PDA) have lower lung compliance and require increased ventilator settings to maintain gas exchange predisposing them to more lung injury [3]. **PDA and Lung Development:** While the patency of the fetal ductus arteriosus protects the developing pulmonary circulation from overflow, the patency of the ductus after birth exposes the pulmonary vessels to excessive blood flow and pressure, which can negatively affect the development of the vasculature and alveolar structure, and increase the risk of bronchopulmonary dysplasia (BPD) [4]. Both vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β are key to lung development. Fetal lambs with increased pulmonary blood flow and hypertension show decreased VEGF expression shortly after birth [5]. Decreased expression of VEGF is also seen in preterm infants with severe respiratory distress syndrome and in infants with BPD [6]. In contrast, TGF-β expression is increased in animals exposed to increased pulmonary blood flow and also in infants with BPD [7, 8]. Thus, both VEGF and TGF-β expression are affected by increased pulmonary blood flow and vascular pressure, and this may negatively influence lung development and function. Preterm baboons who had early pharmacologic closure of the PDA with ibuprofen on day 3 had better alveolar development and improved alveolar surface area than animals where the PDA remained open [9]. **PDA and BPD:** Despite the evidence that increased flow and pressure in the developing pulmonary vasculature can affect lung

development, the role of the PDA in the pathogenesis of BPD is not clear. Several epidemiological studies have found an increased incidence of BPD in infants with symptomatic PDA [10, 11], but there are scarce data from prospective randomized clinical trials (RCTs) supporting this association. Closure of the PDA is associated with rapid improvement in lung mechanics [12]. However, two meta-analyses failed to demonstrate a decrease in long-term pulmonary morbidity when prophylactic indomethacin treatment was compared to later treatment of a symptomatic PDA [13, 14]. It is important to note that most infants randomized to the control arm of these trials received indomethacin soon after the symptoms of the PDA appeared and, therefore, were not exposed to the effects of a prolonged increased pulmonary blood flow. A recent meta-analysis showed that PDA treatment with intravenous ibuprofen was associated with an increased risk of BPD compared to treatment with indomethacin. [15]. However, no significant difference in BPD incidence was found in infants who received indomethacin versus placebo. Several RCTs have compared early PDA closure versus delayed treatment when signs of left heart failure are more evident. Even when the time difference between early and late closure was relatively small, most studies have demonstrated that early PDA closure was associated with decreased pulmonary morbidity and duration of mechanical ventilation [13, 16]. Van Overmeire et al. [17] did not find significant differences in respiratory outcome between infants who received 'early' (day 3) compared to 'late' indomethacin (day 7). However, infants were relatively mature and half of the patients in the 'late' treatment group had spontaneous PDA closure by day 9. In a review of the literature, Benitz [18] concluded that there was no evidence that routine closure of the ductus was beneficial in preterm infants. However, this conclusion is not supported by the results of the review that showed a significant decrease in death or chronic lung disease in infants receiving early versus late treatment for their PDA. In a recent RCT, infants with mild signs of PDA were randomized to 'early' treatment with ibuprofen or 'expectant management' receiving placebo [19]. Infants who developed a hemodynamically significant PDA received open label ibuprofen. No significant differences were found in BPD or any other clinical outcome between the two groups leading to the conclusion that infants with mild signs of PDA may not benefit from early PDA treatment. In another RCT conducted in Australia, infants <29 weeks were screened for a large PDA and if confirmed received indomethacin or placebo before 12 h of age. [20] There was no difference in the primary outcome death or abnormal cranial ultrasound or in BPD between the two treatment groups. However, infants receiving early indomethacin had significantly less early pulmonary hemorrhage. The 72 non-randomized infants with a small PDA had an 80% spontaneous PDA closure rate. The main argument for a conservative approach to the PDA is the fact that many will close spontaneously, avoiding the use of drugs or surgery, both therapies associated with significant complications. However, spontaneous PDA closure rate is gestational age dependent, being much lower in the more immature infant who is at higher risk of severe BPD. The two most recent trials suggest that while it may not be advisable to routinely treat relatively small PDAs that are not hemodynamically significant, large PDAs with significant hemodynamic impact should be treated to avoid the acute and long-term consequences of pulmonary overflow. The difficulty is in defining what a hemodynamically significant PDA is.

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Patent Ductus Arteriosus: Noli Me Tangere?

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An increasing number of reports describe that early aggressive treatment of a persistent patent ductus arteriosus (PDA) does not seem to offer many advantages for the preterm baby [1–5]. On the contrary, side effects of nonsteroidal anti-inflammatory drugs, administered either intravenously or orally, may provoke untoward effects on different organ systems [6, 7]. In many centers, the trend to a conservative approach is increasing and to wait longer to allow spontaneous closure in the 1st week of life [8]. Various complications, e.g. intraventricular hemorrhage, may rather be explained as comorbidities of prematurity than consequences of the PDA [9, 10]. On the other hand, in some of the smallest extremely low birth weight infants, an early deterioration may be observed and ascribed to the large left-to-right shunt through the duct and the inability of the heart to cope with the increased volume load [11]. The challenge is to recognize early on those babies who will not close their duct and who will rapidly progress to an increased shunt and flooded pulmonary circulation. Clinical signs, demographic and antenatal factors, ultrasound assessments [12] and cardiovascular biomarkers [13] were all tested in dozens of studies for their predictive and discriminating power to detect the hemodynamically important PDA early. Echocardiography may guide both the need and the effect of treatment [14–16]. Nevertheless, a gold standard for the early prediction of a hemodynamically significant ductus arteriosus seems not yet defined. Indomethacin, ibuprofen and more recently paracetamol have been studied at different postnatal ages in order to find the optimal timing of duct closure [7, 17, 18]. Controversy remains about when, how and if PDA needs to be treated [19, 20]. This issue will probably not be resolved in the coming years. However, recent and ongoing studies are shedding new light on the 'do not touch strategy'.

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Benefits and Risks of Parenteral Nutrition and Suggested Guidelines

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Intravenous nutrition (IVN) is required in very preterm infants to maintain energy supplies and essential fatty acids and amino acids and to establish an anabolic condition. **Glucose:** Standard glucose infusion rates in preterm infants start at ~6–8 mg/min/kg, increasing to 10–14 mg/min/kg for full IVN. This practice, however, often leads to hyperglycemia, as most preterm infants maintain glucose production from gluconeogenesis [1] and glycogenolysis, caused by increased cortisol adrenalin, and glucagon, which reduce insulin secretion and insulin action, increase tissue protein breakdown and activate regulatory enzymes in the gluconeogenic pathway. Intravenous lipid infusions provide carbon that competes with glucose carbon, glycerol that fuels gluconeogenesis [2], and metabolic products of free fatty acids (ATP, AcCoA and

NADH) that activate key gluconeogenic enzymes [3]. Excessive glucose infusion rates (>11–14 mg/kg/min) adversely increase fat deposition, energy expenditure, O_2 consumption and CO_2 production, fatty infiltration of heart and liver and cellular allostatic load [4] with excessive reactive oxygen species that produce inflammation, augmenting cholestatic hepatitis from selective fatty acids in intravenous lipid products [5]. Hyperglycemia also increases the risk of retinopathy of prematurity [6]; insulin could worsen this risk by promoting reactive oxygen species production, while amino acids might help by promoting IGF-1 production, which reduces the risk of retinopathy of prematurity [7]. Tight glucose control with insulin infusions in preterm infants should be used with caution. Insulin actually makes the baby fatter (including fatty infiltration of heart and liver) and increases complications from excess allostatic load and the risk of hypoglycemic episodes [8]. In a study comparing insulin infusion with reduced glucose infusion rates, there was no difference in all age/weight groups on rates of death, sepsis, retinopathy of prematurity, necrotizing enterocolitis, intracranial hemorrhage, chronic lung disease, days in the neonatal intensive care unit or growth [9]. **Lipids:** Standard intravenous lipid infusions start at 0.5–1.0 g/kg/day at birth and increase to 3.0–3.5 g/kg/day over 2–5 days for full IVN. Unfortunately, this frequently leads to hypertriglyceridemia, as preterm infants have maturational deficiency in lipases and low levels of carnitine palmitoyltransferase. Lipid infusion rates are often reduced to 0.5–1 g/kg/day with sepsis, severe lung disease, surgical stress, steroid use, hyperglycemia, cholestasis and chronically reduced carnitine intakes (>2 weeks). There is little scientific evidence to support such practices or to define mechanisms involved and how to manipulate them to promote better fatty acid oxidation. Supplemental carnitine only enhances lipid oxidation when IVN lasts more than weeks as the sole source of nutrition. **Amino Acids:** Fetal animal growth data predict preterm human amino acid requirements of 3.6–4.8 g/kg/day, which are comparable to those obtained by the factorial method [10] that predicts human fetal amino acid requirements of 4 g/kg/day at 24–30 weeks of gestation. All preterm infants should receive intravenous infusion of amino acids of 2–4 g/kg/day starting right after birth. Almost universally, this practice has increased protein balance and reduced hyperglycemia, without consistent evidence for excessive uremia, hyperammonemia, acidosis or high concentrations of potentially toxic amino acids. Only one study has documented such conditions [11]; this study used Aminosyn PF™ rather than the more commonly used TrophAmine™, and severity and types of illnesses were not clearly defined. In contrast, most studies have documented inadequate concentrations of essential amino acids and slower than normal growth rates, including length and head circumference [12, 13]. Clearly, more studies in preterm infants, particularly in those who are sick and/or physiologically unstable, are necessary to determine optimum glucose, lipid and amino acid mixtures and infusion rates.

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Nectrotizing Enterocolitis: The Mystery Goes On

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Necrotizing enterocolitis (NEC) has largely been present in neonatal intensive care units for the past 60 years. NEC prevalence has corresponded with the continued development and sophistication of neonatal intensive care. Despite major efforts towards its eradication, NEC has persisted and appears to be increasing in some centers. The pathophysiology of this disease remains poorly understood. Several issues have hampered our quest to develop a better understanding of this disease. These include the fact that what we have historically termed 'NEC' appears to be several different diseases. Animal models that are commonly used to study NEC pathophysiology and treatment do not directly reflect the most common form of the disease seen in human infants. The pathophysiology appears to be multifactorial reflecting several different pathways to intestinal necrosis with different inciting factors. Spontaneous intestinal perforations, ischemic bowel disease secondary to cardiac anomalies as well as other entities that are clearly different from the most common form of NEC seen in preterm infants have been put into the same database. In the complete article, I describe some of the different forms of what has been called NEC and make some comments on its pathophysiology, where available studies suggest involvement of genetic factors, intestinal immaturity, hemodynamic instability, inflammation and a dysbiotic microbial ecology. Currently utilized approaches for

the diagnosis of NEC are presented and innovative technologies for the development of diagnostic and predictive biomarkers are described. Predictions for future strategies are also discussed.

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Necrotising Enterocolitis: Biomarkers for Early Detection and Diagnosis

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Necrotising enterocolitis (NEC) is the most common and devastating surgical condition that primarily affects preterm infants [1]. It is an acute life-threatening disease that can result in serious long-term complications involving distant organs, especially the brain. Despite its prime involvement of the gastrointestinal (GI) tract, it is often difficult to differentiate NEC from systemic inflammatory conditions such as late-onset sepsis [2]. As the management between NEC and late-onset sepsis is very different with regard to the duration and choice of antibiotics, requirement for transferring to a paediatric surgical centre, prolonged fasting and need for long-term parenteral nutrition, it is important to diagnose NEC early and differentiate it from other infective/inflammatory conditions [1, 3]. Thus, many recent studies have focused on the discovery of novel biomarkers for early detection of bowel injury. It is now known that different categories of biomarkers of NEC exhibit markedly different properties, and conceptually they can be categorised into three main functional groups [1]: (i) non-specific inflammatory biomarkers or mediators, e.g. acute-phase reactants, cytokines, chemokines and cell surface antigens [1, 2, 4–9]; (ii) 'enhanced' non-specific biomarkers, e.g. faecal inflammatory mediators [10, 11], of which the nature of the specimen enhances their tissue specificity, and (iii) gut-specific biomarkers [3, 12]. Each category has its unique set of properties which render them capable of providing different clinical information on the disease [1]. Non-specific inflammatory biomarkers are mediators that are involved in common molecular pathways of inflammation or infection, and they do not specifically differentiate NEC from other infective/inflammatory conditions, e.g. sepsis and tissue necrosis [1, 2, 4–9]. These non-specific biomarkers include acute-phase reactants, e.g. C-reactive protein [2, 7], apolipoproteins and serum amyloid A [4]; cytokines and chemokines, e.g. interleukin-6 and -10, and RANTES (regulated upon activation of normal T-cell expression and secretion) [5], and cell surface antigens, e.g. neutrophil CD64 [2, 6]. Although these biomarkers are non-specific, they are very sensitive during early phases of the illness [2, 4, 6, 9] and may, therefore, be useful for early detection of NEC when combined with other investigations, such as abdominal radiograph or ultrasound [2]. Biomarkers with late-phase changes, e.g. C-reactive protein, may be more useful to monitor the disease progress or predict the development of complications [7, 9]. Enhanced non-specific biomarkers are also non-specific inflammatory mediators, but by virtue of the nature of the specimen (i.e.

stool) provide information representing the intensified inflammatory response localised to a specific organ (i.e. GI tract). In theory, these biomarkers, e.g. calprotectin, S100A12 and lactoferrin, should better distinguish NEC from other systemic infective/inflammatory conditions. Calprotectin, a neutrophil-secreted peptide, was shown to be increased in faecal specimens of infants with NEC [10]. However, previous studies have small sample sizes and revealed conflicting results [10, 11]. In particular, a significant decrease in faecal calprotectin concentrations has also been reported in fulminant NEC cases [11]. In addition to the difficulty in defining an optimal cutoff concentration, other limitations include: difficulty in obtaining adequate stool samples in a timely manner because of intestinal ileus, likely heterogeneous distribution of the biomarker in stool samples and normal turnover of peptides in the GI tract resulting in significant overlap in faecal concentrations between infants with and without NEC [1]. Thus, although conceptually attractive, these biomarkers have not yet seen widespread clinical use. Recently, there has been intense interest in investigating the use of gut-specific proteins, which are largely or exclusively expressed in GI cells [3, 12, 13]. As these biomarkers are considered tissue specific, they are expected to be capable of differentiating intra-abdominal inflammation, as in NEC, from systemic infection [1, 3]. However, plasma and urine concentrations of many gut-specific proteins, e.g. intestinal fatty acid binding protein (FABP), liver-FABP, trefoil factor-3 and claudin-3, are increased only in infants with severe, widespread GI inflammation [3]. The combined use of liver-FABP, intestinal-FABP and trefoil factor-3 can help neonatologists to differentiate infants with NEC who ultimately require surgery from those with late-onset sepsis or NEC infants who do not require surgery [3]. Though gut-specific proteins are generally considered to be specific for bowel injury, they neither have a high enough sensitivity in the early phase to serve as 'early warning' biomarkers for NEC nor are they able to reliably diagnose the mild cases [3]. In conclusion, many new biomarkers have emerged over the past years. Each category of NEC biomarkers has unique characteristics that render them useful in different phases of the disease. The strengths and limitations of these biomarkers complement each other and underscore the need for further investigation utilising carefully chosen panels for diagnosing and managing NEC infants.

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Breast Milk, Probiotics and Lactoferrin in Newborn Care: What Is the Evidence?

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Breastfeeding is associated with multiple health benefits and, with few exceptions, breastfeeding is recommended for all babies. However, observational studies are highly susceptible to con-founding, hence a causal relationship between breastfeeding and many positive health outcomes remains uncertain. As it would be unethical to randomise infants to breast or formula feeding, inno-vative stratagems are required to address these uncertainties. One novel approach for improving inferences of causality from obser-vational studies is by comparing cohorts from high-income with low- or middle-income countries, as confounding influences in these respective settings are likely to differ; this approach suggests that breastfeeding results in improved intelligence quotient, but not in lower blood pressure or body mass index [1]. In the PROBIT (Promotion of Breastfeeding Intervention Trial) cluster ran-domised trial (ISRCTN37687716) involving over 17,000 healthy full-term infants, hospitals were randomised to deliver the Baby-Friendly Hospital Initiative to promote and support breastfeeding developed by the World Health Organization and United Nations Children's Fund (experimental group) or to continuation of exist-ing breastfeeding policies (control group) [2]. Exclusive breast-feeding and breastfeeding duration were substantially improved in the experimental group (43 vs. 6 and 7.9 vs. 0.6% were exclusively breastfed at 3 and 6 months, respectively) and infants in this group had less gastrointestinal infection and atopic eczema in infancy [2], and improved cognitive development at age 6.5 years [3]; however, overweight or obesity up to 11.5 years were not reduced [4], nor were effects identified on blood pressure or metabolic indices [5]. This conclusion is in accord with our recent data in which, using a direct measure of adiposity, we found no differences between breastfed and formula-fed infants up to 2 months [6], and a sys-tematic review and meta-analysis of world literature indicating that over the first 6 months, healthy, full-term breastfed infants are more adipose than formula-fed infants [7]. Maternal milk is wide-ly held to reduce the risk of necrotising enterocolitis in preterm babies, however, good evidence is lacking to conclude that there is similar efficacy for pasteurised human donor milk when used as a supplement to maternal milk (risk ratio 1.96, 95% CI 0.82–4.67) [8]. Post hoc analyses of follow-up data from preterm babies re-cruited to nutritional trials in the early 1980s also suggest positive effects of human milk on intelligence and metabolic markers de-spite slower growth velocity [9, 10]. Studies such as these demon-strate the inadvisability of employing growth as an outcome mea-sure in infant nutrition studies, and reinforce the importance of identifying reliable biomarkers of long-term health and the ad-visability of designing trials to evaluate functional outcomes wherever possible. The international neonatal community has been enthusiastic in researching the use of probiotics in the pre-term population. Twenty-four randomised trials are included in a Cochrane systematic review and meta-analysis published in 2014 [11]. Significant reductions are shown in severe necrotising en-terocolitis [stage II or more; relative risk (RR) 0.43, 95% CI 0.33–0.56; 20 studies, 5,529 infants] and mortality (RR 0.65, 95% CI 0.52–0.81; 17 studies, 5,112 infants), but curiously there is no evi-dence of a significant reduction in sepsis (RR 0.91, 95% CI 0.80–1.03; 19 studies, 5,338 infants). Reassuringly, there are no reports of systemic infection with the supplemental probiotic, but sadly only 3 trials did not involve the use of formula, and no trial reports any planned assessments of longer-term clinical outcomes or mechanistic evaluations. It is also important to note that results from the largest trial to date, the UK PiPS study (ISRCTN05511098) have yet to be incorporated. To date, trials vary substantially in enrolment criteria, baseline rates of necrotising enterocolitis, pro-biotic type, time and duration of administration, dose and feeding regimen, and long-term effects on immune function and metabo-lism that might ensue when a maternally derived intestinal micro-biome is replaced with an exogenous strain remain wholly uncer-tain. For the moment, therefore, attempts to advocate for universal use in preterm babies as a standard of care appear premature. Lac-toferrin, a mammalian milk glycoprotein, is another proposed ap-proach to prevent sepsis and necrotising enterocolitis in preterm neonates. A Cochrane meta-analysis indicates that oral lactoferrin prophylaxis reduces the incidence of late-onset sepsis in infants weighing less than 1,500 g, but evidence for a reduction in necro-tising enterocolitis is insufficient, as is the efficacy of the combina-tion of lactoferrin with probiotics [12]. The cardinal source of pro-biotics (to say nothing of prebiotic oligosaccharides, lactoferrin, lysozyme, immunoglobulin and other immunologically active molecules that are to be found in colostrum and breast milk) is a baby's mother. It, therefore, seems not unreasonable to suggest that it would be well for the neonatal community to match enthu-siasm for 'off-the-shelf' probiotics and other anti-infective thera-pies with equal enthusiasm for providing maternal colostrum to preterm babies as soon as even a few drops are available, and to follow this with feeds of fresh maternal milk. Remarkably, there is substantial variation in the extent to which preterm neonates re-ceive maternal milk. For example population-based data from England analysed by the Neonatal Data Analysis Unit show a threefold variation in any breastfeeding at discharge among babies born below 30 weeks of gestation, indicating that many neonatal units could achieve much greater breastfeeding success [13].

Health care professionals have an obligation to reduce uncertainties in care and to introduce safe, efficacious and effective therapies without delay. Adequately powered, high-quality trials have rightly been embraced with enthusiasm. However, I suggest that in preterm care we also have other major obligations. We need to improve the all too often extraordinarily poor availability of colostrum and maternal milk, especially for the most vulnerable babies. We need to develop mechanisms to ensure that all infants recruited to trials or receiving inadequately evidenced therapies, receive long-term follow-up designed to test specific hypotheses relating to safety, later outcomes and biological effector mechanisms. We need to promote basic science research in newborn medicine to understand causal pathways as enthusiastically as we have embraced randomised controlled trials. Not least, I look forward to a day when the regulatory environment facilitates the conduct of international trials of promising new therapies, as well as comparative effectiveness research of treatments already in wide use, much more readily, rapidly and rationally than is presently the case [14].

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Diagnosis and Management of Hypotension in the Preterm Infant

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A very large proportion of preterm infants continue to receive intervention for hypotension in the immediate transitional period. A number of national and international surveys [1–3] highlight the continued reliance on mean blood pressure values to guide intervention, despite a lack of good quality evidence to support this intervention criterion [4]. Numerous normative blood pressure reference ranges exist, but these ranges are remarkable only by their significant variability [5–7]. One common definition is a mean blood pressure <30 mm Hg, which is physiologically implausible across such wide gestational age ranges [8]. A blood pressure-based approach to the diagnosis and management of hypotension is the current standard, primarily because of historical precedence and the fact these values are readily available at the bedside, either continuously or intermittently, and the effects of an intervention can be easily evaluated. Other parameters of cardiovascular well-being are not so readily available or necessarily as reproducible at the bedside. These include clinical evaluation (heart rate, capillary refill, colour and level of activity), point-of-care biochemical parameters (base deficit and lactate), point-of-care functional echocardiography, near-infrared spectroscopy and more recently methods of non-invasive cardiac output monitoring. Each of these methods have their own inherent limitations, but it is probable that these forms of assessment in conjunction with blood pressure values will provide a better global assessment of circulatory well-being than blood pressure values alone [9, 10]. The general assumption is that a low blood pressure equates to low blood flow and hence the risk of both short-and long-term adverse outcomes in preterm infants with limited capacity for cerebral autoregulation [11]. However, the relationship between low blood pressure and adverse outcome is not consistent [12–14]. A number of studies have documented a worse outcome in preterm infants with low blood pressure, and undoubtedly the lower the mean blood pressure, the greater the risk of an adverse outcome. Data from the Canadian Neonatal Network highlighted a worse outcome in extremely preterm infants when the mean blood pressure was <20 mm Hg and even more so when the mean blood pressure was <15 mm Hg [15]. More recently, Batton et al. [16] examined 15 different definitions of hypotension in a large cohort of extremely low gestational age preterm infants and were unable to identify a relationship between any of the definitions chosen and adverse outcome. The contrasting findings from these studies are not surprising as the definitions of low blood pressure varied from study to study, and blood pressure alone may be a poor surrogate marker of end organ perfusion [17]. The only consistent finding from the surveys of practice to date is that a mean blood pressure less than gestational age is the most common criterion used to initiate intervention, and that the most common intervention is volume administration followed by dopamine therapy [1, 2]. Dopamine has been in use in newborn care for almost 40 years, is one of the most studied agents in this population of infants and has been the subject of 19 randomised controlled trials to date. However, despite numerous studies in this area, none have been adequately powered

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to address clinically relevant end points, namely death, ultrasound abnormality or long-term neurodevelopmental outcome in this vulnerable group of infants. A recent feasibility study highlighted some of the potential problems in conducting such trials [18]. Despite identifying 119 extremely low gestational age newborns with low blood pressure, only 10 patients were ultimately enrolled. Difficulties included lack of clinician equipoise and refusal of parental consent. Despite these difficulties, the problem still remains and needs to be answered. The ultimate goal in the management of newborn hypotension should be to maintain or restore effective tissue perfusion and this should be assessed on a continual basis by monitoring a combination of clinical, biochemical and haemodynamic parameters. A number of important trials in this area are now underway, comparing different definitions of hypotension and different interventions. These include (1) TOHOP (Treatment of Hypotension of Prematurity); (2) HIP (Hypotension in the Preterm Infant) [19], and (3) NEOCIRC (Neocirculation). It is hoped that these trials will provide clinicians with a greater understanding of the diagnosis and treatment of hypotension in the preterm infant during neonatal transition.

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Caffeine and Inhaled Steroids in the Very Preterm Infant: Time for Prophylaxis?

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Pediatric off-label drug use in hospitals remains very common [1]. Among pediatric patients, the percentage of unlicensed and off-label drug use is highest in neonates [1]. Thus, high-quality neonatal clinical drug trials with sufficient sample sizes to allow firm conclusions are needed, not only for the investigation of new and future drugs but also for old products that are widely used in clinical practice without sufficient data on efficacy and safety, such as inhaled steroids for the prevention and/or treatment of bronchopulmonary dysplasia (BPD), for example [2]. Another example of a drug that has been used for more than 40 years and until 2006 was one of the most commonly prescribed drugs in neonatal medicine, with only a few relatively small and short-term studies supporting its use, is caffeine, a methylxanthine and nonspecific inhibitor of adenosine receptors. It is thanks to the efforts of Barbara Schmidt and the Caffeine for Apnea of Prematurity (CAP) Trial Group that we now have high-quality and reliable data not only on the short-term but also on the long-term outcomes of caffeine use for apnea of prematurity [3–5]. CAP is an international, multicenter, placebo-controlled randomized trial that was designed to determine whether survival without neurodevelopmental disability at a corrected age of 18 months is improved if apnea of prematurity is managed without methylxanthines in infants at high risk of apneic attacks [3]. Infants with birth weights of 500–1,250 g were enrolled during the first 10 days of life if their clinicians considered them to be candidates for methylxanthine therapy [3]. The most frequent indication for therapy reported in CAP was treatment of documented apnea, followed by the facilitation of endotracheal tube removal [6]. Only about 20% of the neonatologists in the trial started caffeine for the prevention of apnea [6]. Thus, the findings of CAP should not automatically be extrapolated to an exclusive prophylactic indication and time for prophylaxis has not come. However, in a recent cross-sectional survey of all neonatologists in Thailand, Lebanon, Australia and a represen-

tative sample in the USA regarding the management of apnea of prematurity with a response rate of 50%, prophylactic methylxanthine use was very common (62%) among neonatologists in all four study locations [7]. The answer to the question whether the time for routine prophylaxis has come for inhaled steroids for the prevention of BPD based on the currently published evidence is 'no'. Nevertheless, a recent survey among pediatricians in chief of all the 343 German pediatric hospitals with a neonatal unit (all levels of neonatal care) indicated that 46% of the responders administered inhaled corticosteroids to premature infants either as prophylaxis or treatment for BPD [2]. The current systematic review from the Cochrane Collaboration focusing on the early administration of inhaled steroids for the prevention of BPD includes seven randomized controlled trials [8]. This review found no statistically significant effect of inhaled steroids on BPD either at 28 days [typical relative risk 1.05 (95% CI 0.84–1.32); typical risk difference 0.02 (95% CI –0.07–0.11)] or at 36 weeks postmenstrual age [typical relative risk 0.97 (95% CI 0.62–1.52); typical risk difference 0.00 (95% CI –0.07 to 0.06)] when data were analyzed either for all randomized infants or only for survivors [8]. No statistically significant differences were noted for mortality or for the combined outcome of mortality and BPD either at 28 days of age or at 36 weeks postmenstrual age. The review identified no statistically significant differences in adverse events between the groups [8]. The authors of this systematic review conclude that 'there is no evidence from the trials reviewed that early administration (in the first two weeks of life) of inhaled steroids to ventilated preterm neonates is effective in reducing the incidence of CLD. Currently, use of inhaled steroids in this population cannot be recommended. Studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of these medications. Studies need to address both the short-term and long-term benefits and adverse effects of inhaled steroids with particular attention to neurodevelopmental outcome' [8]. One study that aims at answering the question whether the early (within 12 h of life) prophylactic use of inhaled corticosteroids (budesonide) in very preterm infants (gestational age 23 0/7–27 6/7 weeks) requiring any form of positive pressure support (mechanical or nasal ventilation or continuous positive airway pressure) increases survival without BPD at 36 weeks of gestational age and also assesses long-term neurodevelopmental outcomes in NEUROSIS (Neonatal European Study of Inhaled Steroids) [9], a randomized placebo-controlled, international clinical trial. Enrollment of approximately 850 infants has finished and results of the study are expected soon.

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Useless and Dangerous Therapies in Neonatology

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The term neonatology has been in existence for about 50 years but expert care of the newborn extends much further back in time [1]. In this review, I will discuss some useless or harmful therapies used in neonatal medicine in the past 200 years. I have drawn on experience and writings of four eminent neonatologists: Bill Silverman [2–4], Alex Robertson [5–7], Alistair Philip [8, 9] and Michael Obladen [10–12]. **Early History – Congenital Syphilis, Thrush and Wet Nursing:** In 1780, a specialised infant hospital was founded in Vaugirard to treat infants with congenital syphilis with mercury administered by nurses' milk [12]. Seventy-nine percent of 1,864 treated infants died but 19% (n = 349) were discharged as 'healed'. Foundling hospitals in the 18th century admitted thousands of newborns each year and less than a third survived their 1st year [10]. These foundlings died from infections, often venereal in origin, but also acquired because of overcrowding and poor sanitation. Thrush or oral candidiasis was rife and probably transmitted by use of wet nurses. Local treatments for thrush included abrasion, astringents, boric acid, vitriol or alum. Effective treatment with nystatin (named after the New York State Department of Health where it was developed) was not available until the 1950s. Wet nursing has been practised from antiquity, availed of by the wealthy and a ready source of income for the poor [11]. It existed only because the wet nurse's baby had either died or was given to a foundling hospital. **1930s and 1940s – Uncontrolled Oxygen, Inappropriate Thermal Care and Withholding Feeds:** Although oxygen had been used earlier to treat apnea and perinatal asphyxia, Bill Silverman said that 'the modern era of treatment (routine prolonged exposure of small premature infants to high concentrations of oxygen) began in earnest… in 1942' [1, 4]. In 1951 the link between uncontrolled oxygen supplementation and retrolental fibroplasia, now known as retinopathy of prematurity, was first recognised. The Cooperative Study (1955) was interpreted as showing

that <40% oxygen was safe for preterm infants. It took another 5 years to discover this was flawed and the reduction to <40% was said to have increased mortality of infants with the respiratory distress syndrome and cerebral palsy in survivors [1]. Even today, uncertainty remains about safe targets for oxygenation of very preterm infants [13]. Similarly, flawed interpretation of research studies allowed preterm babies to be nursed in 'subnormal temperatures' as it was 'believed to be a characteristic of prematurity' [1]. A randomised controlled trial by Bill Silverman in 1959 showed much better survival of infants in incubators at 32°C compared to 29°C and 'it is impossible to know how many babies died from inappropriate environmental temperature during the approximately 50 years before newborn temperature control was understood' [1, 5]. Fear of aspiration led to the practice of withholding feeds for 72 h in preterm infants [1]. From the 1960s, there were concerns that delayed feeding was associated with an increased risk of neurodevelopmental problems and cerebral palsy, which may have been due to hypoglycemia and hyperbilirubinemia. Even today, undernutrition of preterm infants may persist although 'remarkable improvements in mortality over the last 50 years are mostly attributable to adequate nutrition, appropriate temperature control, antibiotics and ventilation methods' [5]. **1950s and 1960s – Chloramphenicol, Hexachlorophene and Epsom Salt Enemas:** Chloramphenicol was given prophylactically to newborns at risk of infection in the 1950s but mortality in preterm infants increased from 29 to 144 per 1,000 after its introduction for preterm rupture of the membranes [1]. Over 10% of infants treated with chloramphenicol died of 'grey baby syndrome', which typically developed a few days after starting treatment. After reducing the dose from 100–150 to 20–50 mg/kg/day, about 1,960 cases of grey baby syndrome disappeared [6]. Toxicity was due to impaired glucuronidation and reduced renal excretion allowing the drug to accumulate. Another drug with toxic effects was hexachlorophene used as a 3% solution to bathe infants to prevent staphylococcal skin colonisation [6]. Neurotoxicity was first reported in 1959 about 7 years after its introduction, and in 1971 the American Academy of Pediatrics recommended an end to hexachlorophene baths. In 1964, Epsom salt enemas were reported to be 100% effective in the treatment of the respiratory distress syndrome on the basis of a consecutive series of 28 preterm babies [2]. Magnesium toxicity also occurred with at least 1 neonatal death but as sporadic use continued until the mid-1970s, there 'is no way of knowing how many babies died as a result of its use' [6]. **Sodium Bicarbonate, Benzyl Alcohol as an Excipient and BPD with Steroids:** Sodium bicarbonate has been used for a long time to treat neonatal cardiac arrest and metabolic acidosis with standard practice being correction of acidosis before giving epinephrine during cardiopulmonary resuscitation [14]. Doubts about bicarbonate therapy were first raised in the 1980s when animal studies showed detrimental effects on myocardial function and reduced likelihood of successful resuscitation. There are no studies in neonates showing either short- or long-term benefits of sodium bicarbonate after cardiac arrest [14]. There is also insufficient evidence that infusions of sodium bicarbonate reduce morbidity or mortality of preterm infants with metabolic acidosis. Thus, bicarbonate is 'basically a useless therapy' [14]. Benzyl alcohol used as an excipient may be more than useless as severe metabolic acidosis, renal and hepatic failure with neurologic signs and gasping respiration occurred in some preterm infants given saline flushes containing 0.9% benzyl alcohol [1]. In 1982, the Food and Drug Administration recommended that flush solutions should no longer contain benzyl alcohol or any other preservatives, and the gasping syndrome disappeared. BPD has been a major concern in neonatology since the late 1960s [9]. High oxygen concentrations and peak inspiratory pressures were implicated in causation of 'classical BPD' and 'new BPD' began to replace it after introduction of surfactant treatment in the 1990s [9]. Of many therapies introduced to treat or prevent BPD, corticosteroids are probably the most notorious [1]. Dexamethasone was first used in the late 1970s to treat severe BPD and 2 early studies suggested short-term benefits in ventilator-dependent infants when very large doses were given (0.5 mg/kg/day). Soon, further trials of dexamethasone to prevent BPD in preterm infants were performed and by the late 1990s over 4,000 had been enrolled in randomised controlled trials [1]. Once long-term outcomes had been assessed after 1998, it became clear that treatment with dexamethasone in the 1st week was associated with a 75% increased risk of cerebral palsy [1, 15]. Thus, dexamethasone has good short-term benefits but adverse long-term effects if given soon after birth in relatively high doses. Whether lower doses or other steroid drugs, including inhaled drugs, used after 7 days when BPD is evolving, are effective and safe remains to be confirmed [1]. **Conclusion:** Introduction of new therapies into neonatal medicine should be based upon the results of large randomised controlled trials with appropriate long-term outcomes in infancy, if not childhood [1].

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Can Brain Cooling Be Optimized by Xenon or Other Interventions?

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Perinatal asphyxia severe enough to cause moderate-to-severe encephalopathy occurs in about 1–2/1,000 births in resource-rich countries with a more than 10-fold greater rate in countries with limited resources [1]. There is a high risk of death and cerebral injury in survivors. It is an important public health problem globally, has large opportunity costs for the affected families and health services, and leads to major litigation claims. Moderate hypothermia is the first therapeutic intervention shown to improve neurological outcomes following perinatal asphyxia [2]. It has been endorsed by professional organisations and rapidly became the standard of care in several high- and mid-resource countries [3], but its role in resource-poor countries still needs to be elucidated [4]. Moderate hypothermia improved clinical outcomes in adults following out-of-hospital cardiac arrest and continues to be investigated for neuroprotective treatment after stroke and head injuries. However, the efficacy of moderate hypothermia following cardiac arrest in adults has recently been questioned after a large study found no significant differences in survival and short-term neurological outcomes in unconscious individuals with presumed cardiac cause treated at a core temperature of 36 or 33°C [5]. Several high-quality randomised controlled trials confirmed that moderate hypothermia after perinatal asphyxia improves neurological outcome in early childhood (up to 2 years of age), but data are scarce about longer-term outcomes. Until recently, two studies have reported results in middle childhood: the CoolCap study of selective head cooling reported parental questionnaire data from 62/135 (46%) survivors at 7–8 years and so was underpowered to examine the effect of hypothermia on cognitive function at higher age [6]. The Childhood Outcomes after Hypothermia for Neonatal Encephalopathy study (NICHD study) achieved a high follow-up rate at 6–7 years, and reported lower mortality in the hypothermia group compared with the control group, but no significant differences in rates of disability or cognitive outcomes, probably due to lack of power [7]. Whilst waiting for the data from the largest trial of moderate hypothermia after perinatal asphyxia, the TOBY trial of moderate whole-body hypothermia, the lack of conclusive clinical trial evidence of continuing neurological benefit after therapeutic hypothermia raised doubt as to whether there are long-term benefits of intervention after perinatal asphyxia. The TOBY Children study will shortly report outcomes of 280 (86%) participants at 6–7 years of age in the TOBY trial. It found that children allocated hypothermia were significantly more likely to survive with an IQ ≥85, and the rates of cerebral palsy and moderate/severe disabilities were reduced in survivors, but the rate of death was similar in the hypothermia and control groups. Combining the results of the TOBY and NICHD studies confirms that moderate hypothermia results in improved outcomes in middle childhood. Following perinatal asphyxia despite treatment with hypothermia, the rates of death (~29%), cerebral palsy (~23%) and cognitive deficiency (~35%) in survivors remain high so additional therapies are needed, and several therapies targeting known pathophysiological pathways involved after perinatal asphyxia are under study [8]. Since large clinical trials will be needed to confirm efficacy, it is essential that robust preclinical and early clinical data underpin the development of new therapies. One promising additional therapy is xenon. Xenon, a monoatomic gas with high tissue solubility, may be neuroprotective following asphyxia through different mechanisms: it is a non-competitive inhibitor of the NMDA subtype of the glutamate receptor and reduces apoptosis probably by up-regulating hypoxia-inducible factor-1α protein and in turn erythropoietin. Experimentally, it reduces cerebral injury in models of hypoxic ischemic injury in different animal species and the neuroprotective effect is stronger when xenon is combined with moderate hypothermia [9, 10]. Preliminary clinical studies suggest that ventilation with 30–50% xenon gas for 18–24 h combined with moderate hypothermia in encephalopathic newborns is feasible and appears safe. A preliminary report from the first randomised trial in newborns (TOBY Xe trial) reported that 30% xenon reduces seizures, though seizures recurred transiently when xenon was discontinued [11]. This trial will complete at the end of 2014 and the results of the early outcomes expected soon after.

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Early and Late Complications of Germinal Matrix-Intraventricular Haemorrhage in the Preterm Infant: What Is New?

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Germinal matrix-intraventricular haemorrhage (GMH-IVH) remains a serious problem in the very and extremely preterm infant. The complete article reviews current methods of diagnosis, treatment and neurodevelopmental outcome in preterm infants with low-grade and severe GMH-IVH. **Conclusion:** There is still no consensus on timing of intervention and treatment of infants with GMH-IVH, whether or not complicated by post-haemorrhagic ventricular dilatation. The discrepancies between the studies underline the need for international collaboration to define the optimal strategy for these infants.

The complete review will be published in *Neonatology*, vol. 106, no. 4, 2014.

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Insulin-Like Growth Factor-1 and Anti-Vascular Endothelial Growth Factor in Retinopathy of Prematurity: Has the Time Come?

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The Doctor's Dilemma: Serial Biomarkers in the Accurate Diagnosis of Early-Onset Sepsis

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Early-onset sepsis (EOS) is associated with high global costs and a major cause of neonatal mortality and morbidity. In addition, sepsis is associated with adverse neurodevelopmental outcomes especially in preterm infants. Many factors make the diagnosis of EOS challenging, including maternal antenatal antibiotic use and the small volumes of blood for culture [1]. Less than 1% of newborns have blood culture-proven EOS [2] and signs of clinical sepsis are non-specific. Most clinicians commence treatment while awaiting culture results due to the hazard of untreated sepsis, which can be rapidly progressive and which can increase morbidity and mortality. The use of antibiotics is potentially harmful, especially in preterm infants with a higher risk of drug toxicity due to hepatic and renal immaturity and an increase in antibiotic resistance. The difficulty with newborns is that their in utero infection status is often unknown at birth. Some information can be gleaned from the placental histology and degree of maternal and fetal inflammatory responses but is not available immediately. The relative 'dose and duration' of exposure to infection differs in each case but is difficult to quantify. Recently, lipopolysaccharides have been measured in cord blood from term and preterm infants, and in the former have been found to be markedly elevated irrespective of the mode of delivery [3]. If a baby passed through an infected birth canal the time taken for the pathogen to reach the bloodstream and allow detection by blood culture or PCR is unknown. Newer techniques for bacterial identification such as PCR or dsRNA may aid in the accurate diagnosis of EOS but are not used in routine practice. Surrogate inflammatory markers such as white blood cell count, immature-mature neutrophil ratio, C-reactive protein and calcitonin are often used in clinical practice to aid decision making in newborns at risk of sepsis. Serial measurements of these markers have a higher positive predictive value for EOS than a single measurement. Serial C-reactive protein measurements have been validated in EOS especially including a measurement at >18 h of age. Mikhael et al. [4] recently demonstrated that serial neutrophil counts over 24 h have high specificity and negative predictive value in term and preterm neonates (n = 2,073). They suggest using these measures with 2 blood cultures to allow early cessation of antibiotics resulting in savings in cost and fungal infection. These neutrophil counts and other published studies have used manual differential counts; in the future, use of computer-generated differential counts using flow cytometry may be useful. However, current automated granulocyte norms are inappropriate for evaluating EOS in newborns and need larger studies for validation [5]. George Bernard Shaw's play written in 1908, *The Doctors' Dilemma*, explores the issues of private medical practice, equality of health care delivery and high-risk therapies and advocate evidence-based practice [6]. The play highlights the doctors' dilemma in treating infection and selecting the correct treatment without overutilising scarce resources. Routine use of serial biomarkers may reduce this dilemma by minimizing antibiotic exposure but ensuring adequate antimicrobial cover for those infants at risk.

References

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Neonatal Thrombocytopenia and Platelet Transfusion – A UK Perspective

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Five percent of newborn infants admitted to UK neonatal units during a recent study developed a platelet count $<60 \times 10^9$/l, and 60% of these were transfused platelets. This review summarises the common causes and mechanisms of thrombocytopenia in the newborn. Relevant evidence relating the platelet count to the risk of haemorrhage is reviewed, and current UK guidance on transfusion thresholds outlined. The UK policy for the provision of platelets for transfusion to neonates is described, including the particular requirements for neonatal allo-immune thrombocytopenia. Finally, we look towards the future and prospects for reducing the need to expose newborns to donor-derived platelets.

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Evidence-Based Advances in Transfusion Practice in Neonatal Intensive Care Units

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