Neonatal intensive care 1

Towards evidence-based resuscitation of the newborn infant

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Effective resuscitation of the newborn infant has the potential to save many lives around the world and reduce disabilities in children who survive peripartum asphyxia. In this Series paper, we highlight some of the important advances in the understanding of how best to resuscitate newborn infants, which includes monitoring techniques to guide resuscitative efforts, increasing awareness of the adverse effects of hyperoxia, delayed umbilical cord clamping, the avoidance of routine endotracheal intubation for extremely preterm infants, and therapeutic hypothermia for hypoxic–ischaemic encephalopathy. Despite the challenges of performing high-quality clinical research in the delivery room, researchers continue to refine and advance our knowledge of effective resuscitation of newborn infants through scientific experiments and clinical trials.

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This is the first in a **Series** of three papers about neonatal intensive care

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Introduction

Although the transition from fetal to newborn life involves considerable changes to the infant's cardiovascular and respiratory systems, most newborn infants adapt without assistance. About 3% of newborn infants need positive-pressure ventilation at birth, fewer infants will receive endotracheal intubation, and cardiac compressions or epinephrine administration are needed in less than 1% of births.[1–3] Nevertheless, WHO estimates that one million newborn infants die from peripartum asphyxia each year. Children who survive asphyxia have a high risk of long-term neurological disability. Effective resuscitation of newborn infants has the potential to improve survival free of disability.

In this Series paper, we will summarise the evidence supporting existing resuscitation techniques and post-asphyxial care for newborn infants. Much of the included research has been undertaken in high-income countries, and we recommend against extrapolation of these results to clinical settings in low-income and middle-income countries. To provide a broad overview of neonatal resuscitation, we have included many important studies and systematic reviews. We have not undertaken an original systematic review or attempted to perform original pooled analyses of data for each included topic. Related topics, including surfactant administration, mechanical ventilation, and non-invasive respiratory support after resuscitation, are discussed in an accompanying paper in this Series by Owen and colleagues.[4]

The physiological transition from fetal to newborn life

Caring for infants during the transition from fetal to newborn life is challenging because the airways are initially liquid-filled and pulmonary blood flow is low. However, as the lungs aerate, there are risks of over-distension, lung injury, and hyperoxia. Awareness of the physiological processes that an infant undergoes during transition to newborn life is essential to providing safe and effective care.

Aeration of the newborn lung

During fetal life, the lung develops as a liquid-filled organ and gas exchange occurs across the placenta. At birth, the airways are cleared of liquid to allow the onset of pulmonary gas exchange, which triggers the cardiovascular changes underpinning the transition to ex-utero life. Airway-liquid clearance primarily results from the hydrostatic pressure gradients between the airways and surrounding tissue that is generated by inspiration.[5] Each breath produces stepwise increases in end-expiratory lung gas volumes (functional residual capacity [FRC]), which tend to decrease between

Key messages

- Lung aeration and ventilation is the key to neonatal resuscitation; it enables pulmonary gas exchange and, by increasing pulmonary blood flow, underpins the cardiovascular transition at birth
- To guide resuscitation of newborn infants, monitor heart rate and peripheral oxygen saturation by pulse oximetry or electrocardiogram in the delivery room
- Hyperoxia should be avoided during resuscitation; infants born at term (37 weeks' gestation or more) should be initially resuscitated with air (21% oxygen) rather than 100% oxygen
- Routine suctioning of the trachea is unnecessary for infants born through meconium-stained amniotic fluid
- Infants born at term or preterm benefit from delayed umbilical cord clamping after birth; however, evidence is insufficient to guide best practice on how best to manage cord clamping in infants born very preterm who need immediate resuscitation
- Continuous positive airway pressure support immediately after birth is recommended as an alternative to routine endotracheal intubation for infants born extremely preterm (less than 28 weeks' gestation)
- In high-income countries, infants born near term or at term with moderate-to-severe hypoxic–ischaemic encephalopathy benefit from therapeutic hypothermia

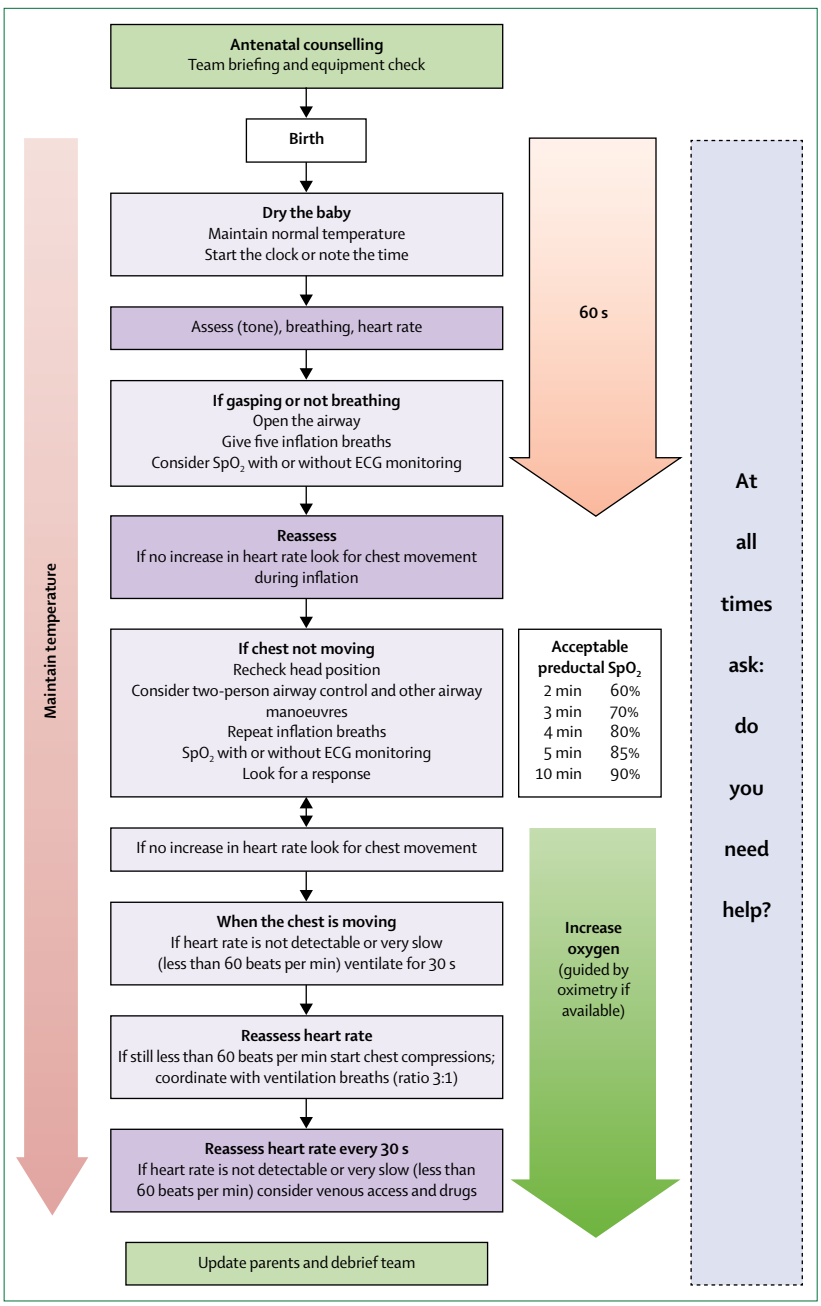

***Figure 1*: Resuscitation Council (UK) Newborn Life Support algorithm, updated 2015**
SpO_2=peripheral oxygen saturation. ECG=electrocardiogram. Reproduced with the kind permission of the Resuscitation Council (UK).

breaths due to liquid re-entry.[5] Overall, airway liquid clearance rates are very high, allowing newborn infants born at term to clear their airways of liquid in three to five breaths.

Recognition that hydrostatic pressure gradients drive airway liquid clearance provided a new understanding of how infants can be assisted at birth. Pressure gradients similar to those generated during inspiration can be applied using positive-pressure ventilation. However, the forces that are imposed with positive-pressure ventilation differ from those of spontaneous breathing, which poses several challenges: (1) because liquid is more viscous than air, high resistance in the liquid-filled airway requires high inflation pressures, but resistance rapidly decrease as the lung aerates; (2) partial lung aeration causes major differences in regional lung compliance, resulting in air preferentially entering aerated regions, potentially overexpanding and injuring those regions; (3) as airway liquid passes into the surrounding lung tissue, pressures within lung tissue rise, increasing the likelihood of liquid re-entering the airways during expiration; and (4) as gas exchange can only commence once the distal airways have aerated, it is possible to ventilate the conducting airways without achieving gas exchange.[5]

The circulatory transition at birth

At birth, lung aeration initiates pulmonary gas exchange and triggers the cardiovascular transition by stimulating an increase in pulmonary blood flow.[6] Before birth, pulmonary blood flow is low, and most right ventricular output flows through the ductus arteriosus into the aorta, thereby bypassing the lungs.[7] Most of the left ventricular preload is derived from placental umbilical venous return, passing via the ductus venosus, the inferior vena cava, and foramen ovale. Following umbilical cord clamping after delivery, the supply of left ventricular preload switches from umbilical to pulmonary venous return.[8] Peripheral vascular resistance also increases and, together with the decrease in pulmonary vascular resistance, results in left-to-right shunting through the ductus arteriosus.

Monitoring the transition to newborn life and the response to resuscitation

International clinical guidelines and resuscitation algorithms, such as those issued by the Resuscitation Council (UK) (figure 1), recommend using the newborn infant's breathing, heart rate, and peripheral oxygen saturation (SpO_2) to guide the resuscitation process. Neonatal clinicians must therefore be able to quickly and accurately monitor these signs and ensure that normal ranges for these parameters are defined.

Assessment of infants at birth—Apgar scores

More than 60 years ago, Virginia Apgar[9] formulated her clinical scoring system for newborn infants—a system still used widely today. The total score is derived from five clinical components, each assigned a value from 0 to 2: skin colour, heart rate, response to stimulation, tone, and respiratory effort, recorded at 1 min and 5 min of life, with additional recordings at 5 min intervals if resuscitation is ongoing. Although each item is scored equally, some items can be influenced by events other than asphyxia (eg, response to stimulation, tone, and respiratory effort are all reduced with increasing

prematurity or by sedation). Moreover, a value of 0 for absence of heart rate is more ominous than for any other item.

Apgar scores are correlated with short-term[10] and long-term[11] outcomes in preterm infants (less than 37 weeks' gestation) and infants born at term (37 weeks' gestation or more). However, interobserver agreement of Apgar scores is poor, even when precise heart rate and SpO_2 data are available to the assessor.[12]

Heart rate

Accurate heart rate assessment is crucial during resuscitation efforts. Many resuscitation algorithms for newborn infants recommend intervening in the delivery room when a low heart rate is detected (typically less than 100 beats per min). Likewise, after bradycardia, an increased heart rate is used as a marker of a good response to interventions (figure 1).

Traditionally, clinicians have estimated the newborn infant's heart rate by auscultation with a stethoscope or by palpation of the umbilical cord or peripheral pulses. These methods remain standard in settings where no advanced technologies are available; however, these methods are not as accurate as pulse oximetry and electrocardiogram (ECG), underestimating the heart rate by about 20 beats per minute compared with an ECG.[13]

A pulse oximeter is a simple device that can be attached to the distal limb of a newborn infant. It non-invasively and continuously measures the heart rate and SpO_2. In general, heart rate measured by pulse oximetry correlates well with ECG;[14] however, pulse oximetry might underestimate heart rate during the first few minutes after birth as the circulation transitions.[15] Existing guidelines acknowledge that ECG can be faster and more accurate than pulse oximetry in the first minutes,[16] but evidence to support the use of ECG instead of pulse oximetry to monitor heart rate in preterm infants is lacking.

Oxygenation

Classically, a newborn infant's oxygenation was estimated by the skin colour: pink (oxygenated) versus blue (cyanosed). However, clinical assessment of an infant's skin colour is imprecise and correlates poorly with SpO_2.[17]

SpO_2 detected by pulse oximetry is related to the partial pressure of oxygen in the blood as described by the haemoglobin–oxygen dissociation curve, which is otherwise only attainable through intermittent and invasive blood gas sampling. Pulse oximetry in the delivery room is now recommended whenever resuscitation is anticipated.[18] The probe should be applied to the right hand or wrist to ensure that preductal, and hence cerebral, oxygen saturation levels are recorded. During the first minutes of life, while right-to-left ductal shunting predominates, SpO_2 is higher in the preductal circulation than in the postductal circulation.[19]

Positive-pressure ventilation

Airway-liquid clearance and lung aeration, which allow the establishment of functional residual capacity and delivery of tidal volumes, are essential for gas exchange and successful neonatal transition.[5] If newborn infants fail to breathe adequately after birth, then positive-pressure ventilation should commence. Positive-pressure ventilation is arguably the most important intervention in neonatal resuscitation; clinicians expected to resuscitate newborn infants must be able to perform positive-pressure ventilation effectively.

The choice of positive-pressure ventilation device varies with the availability of a gas supply, the skills of the resuscitator, and the need to deliver positive end-expiratory pressure or continuous positive airway pressure.[5] Self-inflating bags can be used without a gas supply and are the most effective method for reducing mortality from peripartum asphyxia in resource-limited settings.[20] An alternative is the flow-inflating bag, for which a continuous gas supply is needed. Neither of these devices is optimal for stabilising preterm infants who need continuous positive airway pressure because self-inflating bags cannot deliver continuous positive airway pressure, and appropriate, consistent levels of continuous positive airway pressure are difficult to achieve with a flow-inflating bag.

The T-piece device can consistently deliver a set peak pressure and either a set positive end-expiratory pressure or continuous positive airway pressure, but it also requires a continuous gas supply. Inflation pressures are achieved by occluding the positive end-expiratory pressure valve located on the T-piece; when the valve is not occluded, continuous positive airway pressure is delivered. T-piece devices are easy to use and are preferred by both experienced and inexperienced operators.[21] In manikin studies,[22,23] the T-piece device delivers peak pressures and positive end-expiratory pressure more accurately than other devices, thereby delivering more stable tidal volumes, even for inexperienced operators. This is important because excessive tidal volumes can damage the lung.[24] As the T-piece can deliver consistent continuous positive airway pressure, it might be optimal for providing respiratory support to preterm infants at birth. However, none of these devices measures the tidal volume delivered to the infant.

Positive-pressure ventilation is usually delivered using a face mask covering the mouth and nose. The technique requires a tight seal between the mask and the infant's face,[25] which is difficult to achieve and maintain.[26] Excessive gas leakage from the mask can result in loss of applied pressure and tidal volume.[27,28] Unfortunately, neither the delivered pressure[27] nor the amount of chest rise[29,30] correlates well with the delivered tidal volume. Airway obstruction, which occurs in 25–75% of preterm resuscitations, can also impede effective delivery of mask ventilation.[31] Alternative methods of assessing the

effectiveness of positive-pressure ventilation include colorimetric CO_2 detectors of gas exchange during mask ventilation[32] and respiratory function monitors to detect leak and tidal volume delivery.[33] Both methods can improve positive-pressure ventilation performance, but they are not widely available.

Advances in resuscitation practices

Defining the normal range of heart rate and peripheral oxygen saturations

Normal ranges of heart rate and SpO_2 within the first 10 min of life in infants born at term or preterm have been defined using pulse oximetry. These values are now incorporated into resuscitation guidelines (figure 1). Centile charts of SpO_2[34] and heart rate[35] derived from large cohorts of healthy infants who did not receive resuscitation have been published (figure 2). Median heart rate and SpO_2 in healthy infants born at term are slightly higher at each timepoint than in healthy preterm infants; likewise, these median values are higher in infants from vaginal births than in infants from caesarean births.[34] More than half of healthy infants in these cohorts had a heart rate of less than 100 beats per min at 1 min after birth and did not need resuscitation.

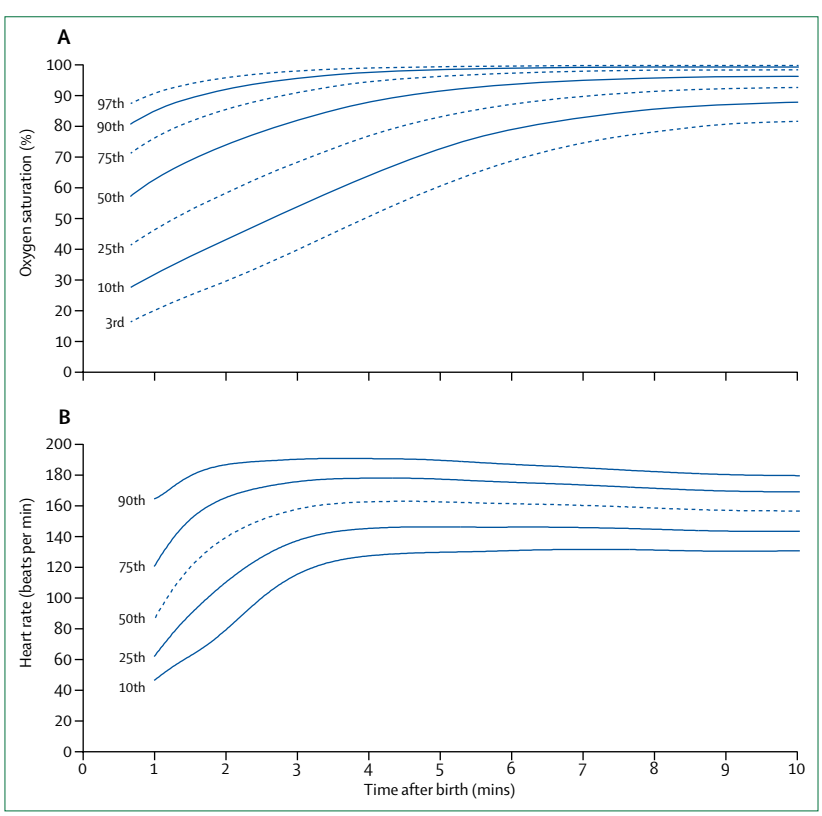

***Figure 2*: Normal ranges of heart rate and $Sp0_2$ within the first 10 min of life in term and preterm infants who received no medical intervention at birth**

Part A was reproduced from Dawson and colleagues,[34] by permission of the American Academy of Pediatrics. Part B was reproduced from Dawson and colleagues,[35] by permission of the BMJ Publishing Group.

Rational use of oxygen therapy in the delivery room

Hyperoxaemia is potentially toxic for human beings. In utero, the fetus is exposed to low relative blood oxygen tension, and infants born very preterm (less than 32 weeks' gestation) are at high risk of hyperoxia-induced injury because the mechanisms to protect against oxygen-free radicals are underdeveloped. When exposed to high oxygen concentrations in the delivery room, even for short periods of time, infants born extremely preterm (less than 28 weeks' gestation) and at term show elevated oxidative stress markers for up to 1 week.[36,37]

Althtough 100% oxygen was once typically used during all newborn resuscitations, neonatal clinicians now limit the infant's exposure to supplemental oxygen from birth onwards. Infants born at term and near term should initially be resuscitated with air (21% oxygen); this consensus is supported by findings from a meta-analysis, which showed that resusication with air reduced mortality in comparison with resusication with 100% oxygen.[38] Although trials of resuscitation with air versus 100% oxygen have been difficult, challenging firmly entrenched beliefs concerning the need for 100% oxygen, the existing guidelines[16] for reducing the starting oxygen concentration highlight the importance of clinical research in this area.

However, there is ongoing uncertainty about the optimal oxygen concentration with which to commence resuscitation of preterm infants. Very preterm infants who are initially resuscitated with air nearly always receive some supplemental oxygen in the subsequent minutes and have low SpO_2 2–10 min after birth.[39,40] An intermediate oxygen concentration, titrated to achieve target saturations while avoiding hyperoxia, might be more appropriate. In systematic comparisons of low versus high initial oxygen concentrations (30% or less *vs* 60% or more) during resuscitation of very preterm infants,[41,42] no differences in the overall rates of death, bronchopulmonary dysplasia, or other important neonatal morbidities were found.

International guidelines[16] now recommend against resuscitating preterm infants with high oxygen concentrations (65–100%), placing instead greater value on not exposing these infants to additional oxygen without proven benefit. Results of an international survey[43] suggest that most clinicians use a starting oxygen concentration of 30%.

Sustained inflations

Sustained inflation is "a positive pressure inflation designed to establish FRC, and applied over a longer period of time than would normally be used to deliver subsequent tidal inflations".[44] The physiological rationale is that sustained positive pressure provides sufficient time to drive lung liquid distally and across the airway wall, aiding transition in infants with inadequate respiratory effort. Despite promising results of 10–20 s initial sustained inflation in intubated animal models,[45,46]

the effects have been less impressive in human infants when the sustained inflation is delivered via a face mask,[47,48] probably because the newborn infant actively closes the glottis during apnoea and hypoxia.[49]

Despite these challenges, clinical studies in preterm infants suggest that sustained inflations applied at birth reduce the chances of the child needing intubation and ventilation in the first few days of life.[50] However, the technique is not recommended in international guidelines, mainly due to a lack of clarity regarding the optimal duration of the inflation. A large international randomised controlled trial of sustained inflation versus standard positive pressure ventilation in extremely preterm infants, with the primary outcome of death or bronchopulmonary dysplasia, is underway.[51]

Tracheal suctioning for meconium-stained amniotic fluid

When distressed, the fetus can pass meconium into the amniotic fluid, which can be inhaled if the fetus gasps in response to hypoxia. Meconium aspiration syndrome occurs when meconium inhaled into the lungs obstructs the airways, either partially or completely, leading to over-distension, air trapping, atelectasis, and inflammation.

The amount of meconium entering the lungs can be reduced by suctioning the trachea immediately after birth, ideally before the first breath. For decades this procedure was recommended for all infants born through meconium-stained amniotic fluid. However, in relatively recent randomised controlled trials,[52,53] no benefit of routine intubation for tracheal suctioning was found for vigorous babies born at term, and suctioning the trachea was only recommended for newborn infants assessed as non-vigorous at birth.

In studies assessing non-vigorous infants born through meconium-stained amniotic fluid,[54,55] routinely suctioning did not affect mortality, risk of meconium aspiration syndrome, or neurodevelopmental outcome at 9 months.[55] Thus, international consensus groups[16] found insufficient evidence to recommend routine intubation for suctioning of meconium in non-vigorous infants, citing potential delays in providing ventilation and potential harm from intubation.

Delayed umbilical cord clamping

Delayed cord clamping results in net placenta-to-infant blood transfer and is now recommended for healthy infants born at term. Delayed cord clamping for at least 60 s after birth, as opposed to early cord clamping, is associated with increased birthweights, increased haemoglobin concentrations at 24–48 h, and increased iron stores at 3–6 months, without increased risk to the mother.[56] However, infants who have delayed cord clamping are more likely to need phototherapy for jaundice, and this is an important consideration in settings where kernicterus is common.

Placenta-to-infant blood transfusion during delayed cord clamping assumes that umbilical venous flow exceeds umbilical arterial flow. However, infants' breathing efforts, crying, and uterine contractions, not time, have been shown to be the major factors affecting flow in the umbilical cord after birth.[57] Findings from animal studies[8] also indicate that commencing ventilation before cord clamping stabilises the cardiovascular transition at birth by allowing the supply of left ventricular preload to immediately switch from umbilical to pulmonary venous return without any reduction in supply. This mitigates the large decrease in cardiac output associated with immediate cord clamping that is caused by a loss of preload.[8] These studies gave rise to the concept of physiology-based cord clamping, whereby the timing of clamping is based on the infant's physiology (ie, whether the infant is breathing), rather than time.[58]

The umbilical cords of preterm infants are usually clamped and cut immediately after birth, allowing clinical assessment or resuscitation, or both, to commence. However, apart from the smoother circulatory transition shown in animal studies, delayed cord clamping for 30 s or more for preterm infants also increases blood volumes by up to 25%, especially after vaginal birth.[59] Delayed cord clamping in preterm infants for 180 s, compared with immediate clamping, reduces the risk of intraventricular haemorrhage, necrotising enterocolitis, and blood transfusion for anaemia.[60] Apart from a possible increase in jaundice, delayed cord clamping is not associated with any maternal or neonatal risks in preterm infants, although long-term outcomes have not been described in much detail.[60,61] How best to manage cord clamping in very preterm infants who need early resuscitation remains an topic of investigation, and studies of resuscitation with the cord intact are ongoing. International guidelines[16] recommend delayed cord clamping for preterm infants who do not need immediate resuscitation after birth. The advantages of delayed cord clamping in resource-limited settings, where specialty care for preterm infants can be limited or where maternal anaemia is prevalent, can outweigh the potential risks.

Umbilical cord milking

Umbilical cord milking from the placental end towards the infant is a proposed alternative to delayed cord clamping that allows earlier access for resuscitation. The method involves milking 20–40 cm of umbilical cord, once or several times, either while the cord is attached to the placenta or not. However, little evidence exists in support of the assumption that cord milking is a good alternative to delayed cord clamping.

In infants born at term, early cord clamping with cord milking improves haemoglobin concentration and iron stores at 6 months of age.[62] Results of systematic reviews of cord milking versus immediate cord clamping for preterm infants showed that cord milking reduced mortality, increased initial haemoglobin concentration,

reduced the need for blood transfusion, and reduced the risk of other neonatal morbidities.[63,64] No long-term outcomes have been reported.

In very preterm infants, cord milking, when compared with delayed cord clamping, increases initial superior vena cava flow and right ventricular output and increases initial haemoglobin concentration, temperature, blood pressure, and urine output.[65] Cord milking, compared with early cord clamping, in late preterm infants is associated with improved iron stores at 6 weeks but also increases the risk of needing phototherapy for jaundice.[66] In one study comparing cord milking with delayed cord clamping,[67] no differences in neurodevelopmental outcomes were found. Cord milking should be assessed in physiological studies and clinical trials and ought to include long-term neurodevelopmental outcomes.

Early care of extremely preterm infants

Antenatal interventions

Interventions to improve outcomes for extremely preterm infants begin before birth and include attempts to delay or prevent preterm birth using tocolytics[68,69] and antibiotics (in the case of preterm birth, prelabour rupture of the membranes).[70] The aim of delaying preterm birth is ultimately to increase gestation and therefore improve neonatal and long-term outcomes, but also to allow time for antenatal corticosteroids administered to the mother to improve outcome.[71] Transfer of mothers at risk of extremely preterm birth to a tertiary perinatal unit for delivery substantially improves infant outcome.[72] Magnesium sulphate is neuroprotective to the fetus when given to women shortly before very preterm birth, reducing the risk of cerebral palsy by almost a third.[73] 63 women (95% CI 39–172) need to be treated to prevent one case of cerebral palsy.

Temperature in the delivery room

Normothermia should be maintained during stabilisation, as both hypothermia and hyperthermia are associated with adverse outcomes in very preterm infants.[74] In one study[75] of more than 5000 infants born with very low birthweight (less than 1500 g), every degree Celsius decrease in the infant's body temperature while in a neonatal intensive care unit was associated with an increase of mortality risk of 28%.

All newborn infants should be resuscitated beneath a radiant heat source. For extremely preterm infants, plastic covers such as polyethylene wraps and bags or plastic caps can limit heat loss[76] and are widely recommended. However, use of an exothermic mattress in addition to plastic covers increases the risk of hyperthermia.[77]

Cold, dry gases injure the neonatal airway. During their stay in a neonatal intensive care unit, infants needing respiratory support, whether non-invasively or via an endotracheal tube, must receive heated and humidified gases to reduce the risk of hypothermia and increase chances of normothermia.[78]

Avoiding routine mechanical ventilation: continuous positive airway pressure in the delivery room

For decades, the standard stabilisation method for very preterm infants was endotracheal intubation and surfactant treatment in the delivery room, followed by a period of endotracheal ventilation in the neonatal intensive care unit. However, endotracheal ventilation of very preterm infants, particularly for prolonged periods, is associated with bronchopulmonary dysplasia, neurodevelopmental impairment, and death.[79,80] To reduce these risks, neonatal clinicians therefore aim to limit the use of endotracheal ventilation. Avery and colleagues[81] were the first to report that treating very preterm infants with nasal continuous positive airway pressure in the delivery room and beyond was feasible and could reduce the need for intubation and the risk of bronchopulmonary dysplasia without increasing morbidity.

Continuous positive airway pressure, either alone or in combination with brief intubation for surfactant administration (the INSURE technique), can be used in the delivery room for extremely preterm infants as an alternative to routine endotracheal intubation with ongoing mechanical ventilation. In a meta-analysis of four trials,[79] continuous positive airway pressure was associated with a reduction in the composite outcome of death or bronchopulmonary dysplasia. However, caution when applying the results of these studies is suggested as all required antenatal consent.

Post-resuscitation care: therapeutic hypothermia

Hypoxic–ischaemic encephalopathy is encephalopathy from peripartum asphyxia. Moderate-to-severe hypoxic–ischaemic encephalopathy is a complication in 1–3 infants per 1000 at-term livebirths in high-resourced settings and in up to 20 infants per 1000 at-term livebirths in low-resource settings, with worse outcome related to increasing severity of the disorder. Although most newborn infants with mild hypoxic–ischaemic encephalopathy survive without disability, mortality in infants with moderate-to-severe hypoxic–ischaemic encephalopathy is at least 25%, and 25% of these infants develop major impairments, including cerebral palsy and cognitive impairment.[82]

Moderate hypothermia for 72 h after birth is the only effective neural rescue therapy for infants born at term and near-term with moderate-to-severe hypoxic–ischaemic encephalopathy. Hypothermia facilities have been established in tertiary neonatal intensive care units in high-resourced countries.[82] However, international guidelines[83] suggest that these results should be applied with caution in resource-limited settings, and hypothermia should be considered only in facilities with the multidisciplinary expertise, equipment, and protocols. Hypothermia reduces death or major disability at 18 months of age by about 25%, which is sustained to school age.[82,84–86] Hypothermia-treated infants also have reduced brain injury on magnetic resonance imaging.[82]

Hypothermia should commence within 6 h of the hypoxic–ischaemic insult (assumed to be at the time of birth). The radiant warmer is usually turned off during resuscitation to maximise neuroprotection. Evidence for this practice is lacking and, without core temperature monitoring, could cause severe hypothermia and associated adverse effects. International consensus statements recommend that hypothermia treatment be restricted to newborn infants meeting the inclusion criteria used in the randomised controlled trials[82] (panel 1), with hypothermia intiated only after resuscitation and standardised neurological assessment. These criteria include evidence of moderate-to-severe encephalopathy and peripartum asphyxia in infants at an age of 35 weeks' gestation or more.[82] Some clinicians advocate that hypothermia be considered for infants with mild encephalopathy, for late preterm infants with hypoxic–ischaemic encephalopathy, and after postnatal collapse.[88]

The mode, technique, depth, and duration of hypothermia have been studied extensively. Whole-body hypothermia to a core temperature of 33·5°C and selective head cooling for 72 h in both inborn and outborn infants are effective.[89] Extended duration (120 h *vs* 72 h) and increased depth (32°C *vs* 33·5°C) of whole-body hypothermia do not reduce mortality and provide no additional neuroprotection.[90] Continuous core (rectal or oesophageal) temperature monitoring in newborn infants with hypoxic–ischaemic encephalopathy is crucial. Hyperthermia must be prevented, as each 1°C increase in temperature above 38°C is associated with a 4-fold increase in mortality and disability.[91] Uncontrolled cooling should also be avoided as overcooling increases the potential for serious adverse consequences of hypothermia.[92] Adverse effects of moderate hypothermia for hypoxic–ischaemic encephalopathy include sinus bradycardia and thrombocytopenia, and late subcutaneous fat necrosis.[82,93] Hypothermia alters drug metabolism and clearance, thus necessitating dose adjustment for aminoglycosides, morphine, and anticonvulsants.[94]

Despite the neuroprotection afforded by therapeutic hypothermia, almost half of newborn infants with moderate-to-severe hypoxic–ischaemic encephalopathy will die or they will survive with serious neurodevelopmental impairments.[82] Adjunctive therapies are urgently needed; those currently under investigation include erythropoietin, xenon, melatonin, N-acetyl cysteine, allopurinol, and stem cells.[95]

Panel 1: Hypothermia treatment for hypoxic–ischaemic encephalopathy

Criteria for hypothermia treatment

Evidence of moderate-to-severe encephalopathy 1–6 h after birth:

- Any seizures (clinical or electroencephalographic) or
- Modified Sarnat criteria[87] (lethargy, stupor, coma, abnormal tone)
- Presence or absence of abnormal background on amplitude-integrated electroencephalogram

Evidence of peripartum asphyxia (at least one of the following):

- Apgar score 5 or less at 10 min after birth
- Ongoing resuscitation (chest compressions or ventilation) at 10 min after birth
- Acidosis (cord pH<7·0 or base deficit ≥12 mmol/L) within 1 h after birth
- 35 weeks' gestation or more at birth

Contraindications to hypothermia treatment

- Birthweight less than 1·8 kg
- Major (or suspected major) congenital abnormalities
- Overt bleeding (including subgaleal haemorrhage)
- Death is considered imminent

The challenges and ethics of resuscitation research

When prospective consent is required for delivery room interventions, enrolment is limited by the urgency of delivery, the availability of researchers, and the ability of parents to consent immediately before delivery. Mothers who present in active labour and with sepsis, haemorrhage, or other obstetric complications that can increase the risk of adverse neonatal outcome might be less likely to be enrolled, which could limit the generalisability of the results.

These limitations were seen in the SUPPORT trial,[96] in which the use of continuous positive airway pressure was compared with intubation in the delivery room along with different oxygen saturation targets using a factorial design. Trial participation of extremely preterm infants required antenatal consent. A prospectively planned analysis[97] showed that mothers of enrolled infants had substantially different demographics and a high rate of exposure to antenatal corticosteroids compared with mothers of eligible, non-enrolled infants. Non-enrolled infants were small, less mature, in poor condition at birth, and were likely to need advanced resuscitation; consequently, these infants had high rates of mortality and morbidities.[98] Findings from an investigational drug trial[99] also showed that newborn infants who were allocated to receive placebo had better outcomes than infants who were eligible but not randomised—a finding that has been replicated in adult randomised controlled trial participants.[100,101]

These data raise the possibility of using retrospective or deferred consent (also known as waiver of consent) for studies in the delivery room.[102,103] Retrospective consent, by which infants are first enrolled and studied at birth, and consent sought from parents soon after, might diversify enrolment to provide a more representative sample. However, the use of retrospective consent is ethically complex,[104] and the experience of families of newborn infants who have been enrolled in studies using retrospective consent has not been described. Parents should be involved in identifying the most important questions to be addressed through clinical trials in the

Panel 2: Key advances in newborn infant resuscitation

- The use of pulse oximetry and electrocardiogram in the delivery room to monitor the response to resuscitation
- Defining the normal range of heart rate and peripheral oxygen saturations in well newborn infants
- The importance of avoiding hyperoxia, and that term infants should be initially resuscitated with air (21% oxygen) rather than 100% oxygen
- The recognition that suctioning of the trachea is not necessary for infants born through meconium-stained amniotic fluid
- Recognition of the benefits of delayed cord clamping in term and preterm infants
- The use of antenatal magnesium sulphate to reduce cerebral palsy in infants born very preterm
- Continuous positive airway pressure is an alternative to routine endotracheal intubation in extremely preterm infants
- Therapeutic hypothermia for near-term and term newborns with moderate-to-severe hypoxic–ischaemic encephalopathy

Panel 3: Practices that are promising but require further assessment

- The use of colorimetric CO_2 detectors and respiratory function monitors to guide resuscitation
- The ideal intermediate oxygen concentration with which to initiate resuscitation of very preterm infants
- Sustained inflations to initiate resuscitation in extremely preterm infants
- Delayed cord clamping or umbilical cord milking for very preterm infants
- Adjunctive therapies for hypoxic–ischaemic encephalopathy
- The ethics of including retrospective or deferred consent processes in clinical trials in the delivery room

delivery room, in designing the studies, and in membership of ethics committees. These considerations might also help identify those trials that are most suitable for a retrospective consent process.

Conclusions

We have highlighted some of the important advances in newborn infant resuscitation (panel 2) and some of the interventions that are promising but require further assessment (panel 3). Clinicians now demand high-quality evidence to guide neonatal practice, with evidence of efficacy and safety in both the short term (until hospital discharge) and long term (childhood and beyond). High-quality clinical research in the delivery room is challenging but possible. Preliminary basic science and animal studies can guide neonatal clinicians' choice of the most plausible therapies and most important questions to answer in clinical trials.

Contributors

BJM performed the initial literature review, wrote the first draft of the paper, and edited and submitted the paper. LSO contributed to the first draft and edited the paper. SBH, SEJ, JLYC, LWD, and PGD contributed original content and edited the paper. BJM had final responsibility for the decision to submit the paper for publication.

Declaration of interests

We declare no competing interests. PGD declares non-financial support from Fisher & Paykel Healthcare outside the submitted work.

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