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Delivery Room Management of Asphyxiated Term and Near-Term Infants

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Abstract
Approximately 800,000 newborns die annually due to birth asphyxia. The resuscitation of asphyxiated term newly born infants often occurs unexpected and is challenging for healthcare providers as it demands experience and knowledge in neonatal resuscitation. Current neonatal resuscitation guidelines often focus on resuscitation of extremely and/or very preterm infants; however, the recommendations for asphyxiated term newborn infants differ in some aspects to those for preterm infants (i.e., respiratory support, supplemental oxygen, and temperature management). Since the update of the neonatal resuscitation guidelines in 2015, several studies examining various resuscitation approaches to improve the outcome of asphyxiated infants have been published. In this review, we discuss current recommendations and recent findings and provide an overview of delivery room management of asphyxiated term newborn infants.

Introduction

All newborn infants require basic interventions (i.e., drying and stimulation and keeping them warm) during their transition from fetal to neonatal life [1, 2]. Approximately 5% of newborns (6–7 million worldwide per year) need breathing support [1, 2], and 0.1% of term infants and 10–15% of preterm infants (1.5–2.5 million worldwide) need cardiopulmonary resuscitation (CPR) [3–6], defined as chest compressions, 100% oxygen, and/or epinephrine (adrenaline) in the delivery room (DR). Despite receiving CPR, about 800,000 newborns die annually worldwide due to birth asphyxia or intrapartum events. There are a number of causes of birth asphyxia or intrapartum events including poor antenatal healthcare as well as maternal, placental/umbilical, and neonatal issues [7–13] (Table 1).

Birth asphyxia is a condition of impaired gas exchange and lack of perfusion of various organs, which leads to progressive hypoxia, hypercarbia, and metabolic acidosis [9]. Asphyxia is a leading cause of neonatal death and disability. By introducing air instead of 100% oxygen of term or near-term newborns in need of positive pressure ven-

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tilation (PPV) a decade ago, a 30% reduction in mortality was demonstrated [14]. However, still a substantial number of deaths may be preventable by improvements in neonatal resuscitation. Prompt resuscitative measures are needed to prevent cerebral injury by avoiding further hypoxia and ischemia and reversing respiratory and metabolic acidosis [13, 15–17]. The aim of this review is to give an overview of DR management in asphyxiated term and near-term newborn infants.

Umbilical Cord Management

Neonatal resuscitation guidelines state that infants, who require resuscitation measures, should have immediate cord clamping [18]. The European Resuscitation Council Guidelines state that where delayed cord clamping is not possible, cord milking should be considered in infants >28 weeks' gestation [19]. However, the optimal umbilical cord management strategy, which improves outcomes for asphyxiated term newborns, remains unknown [20]. A recent systematic review compared various umbilical cord management strategies including a total of 9,159 women and infant pairs in late preterm (34^{+0}–36^{+6} weeks' gestational age) and term (≥37 weeks' gestational age) infants. Unfortunately, none of the included trials reported on the primary outcome of survival without moderate to severe neurodevelopmental impairment in early childhood. By randomizing vigorous term infants to immediate cord clamping versus umbilical cord milking or to delayed versus immediate umbilical cord clamping, no significant differences in neonatal outcomes (including Apgar scores, need for resuscitation, or admissions to the neonatal intensive care unit) were found [21]. Recently, updated SpO_2 and HR percentiles in term infants with delayed cord clamping were published [22]. They reported on higher SpO_2 and HR values and earlier stabilization compared to term infants with immediate cord clamping [22].

Umbilical Cord Milking

Erickson-Owens et al. [23] randomized 24 vigorous term infants to immediate cord clamping or umbilical cord milking and reported comparable Apgar scores and need for resuscitation, with no admissions. While studies suggest that umbilical cord milking is an alternative to immediate cord clamping in vigorous infants, there is a lack of data in nonvigorous infants. A retrospective analysis of 157 late preterm and term infants (35–42 weeks) with abnormal umbilical cord blood gases (cord arterial or ve-

Table 1. Causes for birth asphyxia and perinatal events [7–13]

Healthcare	Maternal	Uterine/placental	Delivery complications/ umbilical cord	Fetal/neonatal
Low socioeconomic status of the parents leading to inadequate antenatal care	Obesity	Uterine rupture	Labor prolongation	Perinatal arterial ischemic stroke
Poor intrapartum care	Preeclampsia	Placental insufficiency	Precipitous delivery	Fetal exsanguinations due to bleeding
Unskilled birth attendance	Hypertension	Placental infarct/stasis	Shoulder dystocia	Airway anomalies
Lack of availability of proper equipment	Hypotension/shock	Chorioamnionitis	Abdominal wall dystocia	Congenital malformations
Poor neonatal care	Severe anemia	Chronic patchy/diffuse villitis	Narcotics during labor	Cardiopulmonary diseases
Unskilled staff in neonatal resuscitation	Diabetes mellitus	Obstetric hemorrhage	Cord prolapse	Neurologic disorders
Lack of availability of proper equipment	Infection	Placenta previa/accreta	Nuchal cord	Infection/septic shock
	Age ≥35 years	Placental abruption	Cord Knot	Meconium aspiration
	Maternal smoking	Maternal hypertension	Velamentous cord insertion	Multiple gestation
		Substance abuse	Vasa previa	Prematurity
		Uterine overdistention		Twin-to-twin transfusion
		Trauma		Postdates

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nous pH of ≤7.1 or base deficit <−12 mmol/L) reported fewer infants needing resuscitation (38 vs. 56%, $p = 0.07$) and ongoing respiratory support (19 vs. 31%, $p = 0.16$) with umbilical cord milking compared to immediate cord clamping [24]. Girish et al. [25] compared umbilical cord milking with immediate cord clamping in 101 depressed term neonates at birth in a quasirandomized (alternating months) trial and reported no differences in resuscitation delay, resuscitation efforts, and short-term outcomes. There is a multicenter trial examining immediate cord clamping with umbilical cord milking in nonvigorous newborn infants, 35^{+0}–41^{+6} weeks' gestation, currently ongoing (ClinicalTrials.gov NCT03631940).

Physiological-Based Cord Clamping

During physiological-based cord clamping, the infants remain attached to the umbilical cord until gas exchange/lung aeration has occurred, and this might be an alternative to delayed cord clamping and umbilical cord milking; however, there are currently limited data available. Studies using asphyxiated near-term lambs reported that resuscitation with intact umbilical cord (i) markedly improved cardiovascular function by increasing venous return to right atrium and pulmonary blood flow, (ii) mitigated rebound hypertension, and (iii) reduced cerebral vascular leakage compared with immediate or delayed cord clamping [20, 26, 27]. A recent randomized controlled trial in 231 nonbreathing newborn infants compared resuscitation with intact umbilical cord or immediate cord clamping [28]. Peripheral arterial oxygen saturation (SpO_2) was significantly higher in the resuscitation with intact umbilical cord group with a mean (SD) of 90.4 (8.1) versus 85.4 (2.7)% in the immediate cord clamping group. Apgar scores were higher as well in the intact umbilical cord group compared to immediate cord clamping, while heart rate (HR) was lower in the intact umbilical cord group at 1 and 5 min compared to immediate cord clamping [28]. Whether physiological-based cord clamping or resuscitation on the intact umbilical cord will improve the outcome of asphyxiated newborn infants remains unclear.

Heart Rate Assessment

Current neonatal resuscitation guidelines recommend to asses HR immediately after birth using pulse oximetry or electrocardiography (ECG) for ongoing monitoring [18, 29]. Clinical studies reported that inter- and intra-observer variability with auscultation and palpation underestimates HR about 21 and 14/min, respectively [30–32]. Furthermore, neither palpation nor auscultation can provide continuous HR assessment during resuscitation. Hence, continuous, objective, and precise measures are required. Both pulse oximetry and ECG fulfill these criteria with very good accuracy [33]. Due to the delay in obtaining a signal with the pulse oximeter, the ECG provides a more accurate HR in the first 3 min after birth [18]. In 2015, the neonatal resuscitation guidelines recommended routine use of ECG for continuous monitoring of HR during DR resuscitation [34]. The American Heart Association/Neonatal Resuscitation Program (AHA/NRP), however, recommends that "auscultation of the precordium remains the preferred physical examination method for the initial assessment of the heart rate. Pulse oximetry and ECG remain important adjuncts to provide continuous heart rate assessment in babies needing resuscitation" [2].

Pulseless Electrical Activity

The practice change following the ILCOR recommendation of applying ECG primarily to detect HR led to several case reports of pulseless electrical activity in the DR [35, 36]. Pulseless electrical activity is defined as the presence of electrical activity without any associated mechanical activity [35, 36]. Similar animal studies reported pulseless electrical activity in ~50% of asphyxiated neonatal piglets [35, 37–39]. Pulseless electrical activity is caused by hypoxia, hyper-/hypokalemia, hypovolemia, hypothermia, hydrogen ions (acidosis), tension pneumothorax, cardiac tamponade, thrombosis (coronary and pulmonary), and toxins [40]. These reports raise concerns about the use of ECG in the DR, and therefore healthcare providers should be aware of the potential pitfalls with ECG during neonatal resuscitation [35]. A recent case series stated that if a HR is displayed on the ECG but the infant is unresponsive, pulseless electrical activity should be suspected and chest compressions should be started [35]. We suggest to combine auscultation, palpation, pulse oximetry, and ECG in asphyxiated newborn infants, which might be more reliable compared to ECG or pulse oximetry alone [39, 41].

Respiratory Support

In the first 1–2 min after birth, ~60 and 17% of spontaneously breathing term infants have a HR <100 and <60/min, respectively [42]. At 3 min after birth, 7% of these spontaneously breathing term infants still have a

HR <100/min [42]. In spontaneously breathing term infants, it took 1–10 breaths to the first expired CO_2 (ECO_2) and 21–258 s until peak CO_2, suggesting complete lung aeration [43, 44]. Similarly, during PPV, ECO_2 levels are closely related to lung volumes at end inflation, and ECO_2 is first detected when ~7% of the distal lung regions are aerated, and ECO_2 levels increase ~30 s before HR increased >100/min [45, 46].

While these data suggest that an increase in HR might be delayed despite adequate ventilation, the Neonatal Resuscitation Program textbook states that once PPV is started, an increase in HR should be observed within 15 s [47]. However, in severe bradycardic asphyxiated newborn piglets, HR increased only in 50% of piglets after 30 s of adequate PPV [48]. Saugstad et al. [49] reported that the HR of asphyxiated newborn infants was mean (SD) 93 (33) and 113 (30) at 60 and 90 s after birth, respectively. In another study, Saugstad et al. [14] reported that the HR was ≤100/min in approximately 2/3 and 1/6 of depressed newborn infants at 1 and 3 min after birth, respectively. Furthermore, a slow or no increase in HR in the first 3 min of life seemed to represent a poor prognostic sign, giving a 9-fold risk for death within a week [14].

Mask Ventilation

The current neonatal resuscitation guidelines recommend mask ventilation using an appropriate face mask connected to a manual ventilation device [1, 2]. The most commonly used devices to provide PPV in the DR are a self-inflating bag and T-piece resuscitator [50, 51]. A recent systematic review included 3 randomized trials and 1 observational study and reported no significant differences in survival at discharge, air leak, or short- and long-term outcomes [52]. However, mask ventilation with a T-piece resuscitator might result in fewer intubations in the DR and higher rates of survival to discharge [52].

During ventilation, an initial peak inspiratory pressure (PIP) of 30 cm H_2O in term newborn infants should be used [18, 19, 53]. However, the optimum pressure, inflation time, and gas flow required to establish an effective functional residual capacity in depressed newborn infants is unknown. Dawson et al. [50] reported that PIP is a poor proxy for tidal volume delivery and that the PIP must be adjusted during resuscitation as compliance and resistance of the lung is changing rapidly. However, a prompt increase of HR above 100/min can be an important sign of adequate tidal volume generated by the chosen PIP during resuscitation.

The 2-point top hold and the OK rim hold (thumb and index finger form a C-shape) are the most adequate face mask techniques for placing and holding a face mask and minimizing mask leak during PPV [54]. However, several DR studies reported that mask leak and airway obstruction are common during bag and mask PPV in particular in preterm infants [55, 56]. Mask leak and obstruction often remain unrecognized and might delay lung aeration, hence effective gas exchange and increase in HR. In a very recent meta-analysis comparing face mask with nasal cannulae for noninvasive PPV in the DR reported a nonsignificant reduced risk for chest compressions (3 studies, RR 0.37, 95% CI: 0.10–1.33, $p = 0.13$, $I^2 = 28\%$) and a nonsignificant reduction in DR intubation rates (5 studies, RR 0.63, 95% CI: 0.39–1.02, $p = 0.06$, $I^2 = 52\%$) when using nasal cannulae, suggesting to consider the use of nasal cannulae as an alternative to face mask PPV [57].

Intrauterine hypoxia suppresses fetal breathing movements and causes apnea and glottis closure (=airway obstruction) after birth [58]. In preterm rabbits, Crawshaw et al. [58] reported that the glottis only opens during spontaneous breathing movements while it remains closed during apnea, which might result in ineffective PPV [59]. Glottis closure might also be present in term infants; however, this has not been investigated yet.

MR. SOPA

Current neonatal resuscitation guidelines recommend a face mask in combination with a manual ventilation device to provide respiratory support after birth [18, 19]. A tight seal between mask and face and appropriate positioning of the infant's upper airway are important for effective mask ventilation. When infants do not respond to initial inflations, the neonatal resuscitation program (NRP, Houston, TX, USA) and the neonatal life support group (NLS, United Kingdom) suggest a structured approach for escalation of care. MR. SOPA is thought to be used as an acronym for **M** (mask adjustment), **R** (reposition airway), **S** (suction mouth and nose), **O** (open mouth), **P** (pressure increase), and **A** (alternate airway) as a laryngeal mask airway (LMA) or endotracheal tube.

Sustained Inflation

The current European neonatal resuscitation guidelines recommend 5 consecutive 2- to 3-s sustained inflations to initiate PPV [19]. However, there is no clinical evidence that these 5 initial sustained inflations will support lung aeration. Studies in near-term intrauterine asphyxiated lambs demonstrated that a single sustained inflation of 30 s improves the speed of circulatory recovery, carotid blood flow, and cerebral oxygen delivery, and further cardiac contractility increases more rapidly compared to PPV or 5 consecutive 3-s sustained inflations [60, 61]. However, cerebral plasma protein extravasation was increased after a single 30-s sustained inflation, indicating a greater disruption in the blood-brain barrier, which might exacerbate brain injury in asphyxiated newborns [61]. These data suggest that one 30-s sustained inflation might improve lung aeration compared to 5 consecutive 3-s sustained inflations. The 2020 ILCOR neonatal resuscitation guidelines state that for term or late preterm infants who receive PPV for bradycardia or ineffective respirations at birth, it is not possible to recommend any specific duration for initial inflations due to the very low confidence in effect estimates [1].

Oropharyngeal Airway

The oropharyngeal airway was designed to hold the tongue away from the back of the pharynx, thus providing a clear channel/airway for respired gases. The European Neonatal Resuscitation guidelines recommend an oropharyngeal airway during their structured approach for escalation of care [19]. Kamlin et al. [62] randomized 137 infants <34 weeks' gestational age to either mask PPV alone or in combination with an appropriately sized oropharyngeal airway. Overall, obstructed inflations and partial obstruction were more frequently observed in infants stabilized with an oropharyngeal airway (81 vs. 64%, p = 0.03, and 70 vs. 54%, p = 0.04), respectively [62]. The trial included infants <34 weeks' gestation only, which makes translation to term babies difficult. However, healthcare providers should be aware that an oropharyngeal airway might increase airway obstruction during mask ventilation.

Laryngeal Mask Airway

The current neonatal resuscitation guidelines recommend an LMA as an alternative to tracheal intubation during resuscitation of newborn infants >34 weeks' gestation [18, 19]. A recent Cochrane review with 794 newborn infants reported that PPV with an LMA resulted in less need for endotracheal intubation and shorter ventilation time compared to mask PPV (RR [95% CI]: 0.24 [0.12–0.47], I^2 = 34%, and mean difference [95% CI]: −18.0 s [−24.35 to −13.44 s], I^2 = 95%), respectively [63]. Insertion time or failure to correctly place either an LMA or an endotracheal tube was similar [63]. The current evidence suggests that an LMA might be an adequate alternative during resuscitation of a severe asphyxiated term infant. Pejovic et al. [64] compared LMA and face mask during neonatal resuscitation in a low-resource setting and demonstrated that the total ventilation time and the mean time to spontaneous breathing were shorter in newborn infants who were initially resuscitated with LMA. It was suggested that this approach could be very useful especially in DR settings with resuscitation teams without adequate skills in tracheal intubation and/or in low- and middle-resource settings [65]. Pejovic et al. [66] reported that an LMA is safe in the hands of midwives but is not superior over a face mask with respect to the composite of early neonatal death or moderate-to-severe hypoxic-ischemic encephalopathy (HIE) (adjusted analysis for LMA vs. face mask: RR, 95% CI: 1.16 [0.90–1.51], p = 0.26) in low-resource settings.

Oxygen

Oxygen during Respiratory Support

Already a decade ago, studies demonstrated that asphyxiated term infants resuscitated with room air gave their first cry earlier and attained a sustained pattern of spontaneous respiration more rapidly compared to those with 100% oxygen resuscitation [67, 68]. Vento et al. [69, 70] showed that using pure oxygen for neonatal resuscitation increases oxidative stress and causes more damage to organs including the heart and kidneys in severely asphyctic term neonates. For term and near-term newly born infants, the current neonatal resuscitation guidelines recommend 21% oxygen initially during respiratory support and 100% oxygen when chest compressions are started [18, 19, 71, 72]. Supplemental oxygen should then be titrated according to preductal oxygen saturation targets [18, 19, 72]. A systematic review and meta-analysis including 5 quasi-randomized controlled trials and 1,302 newborn infants (median 38 weeks' gestation and most of them moderately asphyxiated) reported that outcomes as time to first breath >3, 5-min Apgar score <7, and survival were better for those resuscitated with room air rather than 100% oxygen [73]. Further, 1 death would be prevented for every 20 newborn infants resuscitated with air rather than 100% oxygen [73]. Hence, room air instead of pure oxygen resuscitation may prevent 200,000 deaths, in addition to 300,000 fresh still births (out of approximately 1 million) who may be rescued by room air ventilation [74].

Chest Compressions

Current neonatal resuscitation guidelines state that if the HR remains <60/min despite adequate ventilation, chest compression should be started [19, 29]. Chest compression should be delivered using a (i) coordinated 3:1 compression:ventilation (C:V) ratio, (ii) at the lower third of the sternum, (iii) a depth of ~1/3 of the anterior-posterior diameter of the chest, (iv) using the 2-thumb encircling technique, and (v) allowing full chest recoil relaxation. However, these recommendations are based on extrapolations from mathematic modeling, animal data, and pediatric and adult studies as there is a lack of neonatal human data.

Chest Compression:Ventilation Ratio

Rationales for using 3:1 C:V include (i) a higher physiological HR of 120–160/min and (ii) breathing rates of 40–60/min in newborn infants compared to adults. Several studies compared different C:V ratios (2:1, 3:1, 4:1, 9:3, and 15:2) in asphyxiated newborn piglets showing that time to return of spontaneous circulation (ROSC) was similar, independently of C:V ratio [75–77]. Schmölzer et al. [78] investigated the approach of chest compressions with nonsynchronized ventilation and reported that tidal volume, time to ROSC, survival, and hemodynamic recovery were similar compared to 3:1 C:V in asphyxiated neonatal piglets.

Chest Compression Rate

A mathematical model suggests that the chest compression rate should be 180/min for term infants [79]. However, this might not be feasible due to methodological limitations and rescuers' increased fatigue with higher chest compression rate. Furthermore, animal studies compared various chest compression rates and reported no difference in time to ROSC or survival [80, 81]. Neither different rates of chest compression superimposed by sustained inflations (90 vs. 120/min) nor different rates of chest compression with asynchronized ventilation (90, 100, and 120/min) showed a benefit regarding time to ROSC and survival in neonatal asphyxiated piglets, although the hemodynamic recovery, cerebral inflammatory, and brain injury markers were improved during chest compression with asynchronized ventilation with a rate of 120/min compared to 90 or 100/min [80, 81].

Depth of Chest Compression

The recommendation regarding chest compression depth is based on extrapolation from CT scans in 54 neonates, which showed that a 1/3 anterior-posterior depth would result in a superior ejection fraction compared to 1/4 or 1/2 AP depth [82]. The main difficulty for resuscitators is the inability to assess the chest compression depth during chest compression. A too shallow anterior-posterior diameter could result in inadequate cardiac output, and a too high anterior-posterior diameter could cause overcompression resulting in rib fractures, cardiac contusion, and thoracic injuries.

Chest Compression Technique

Several manikin studies demonstrated that the 2-thumb encircling technique achieved (i) higher proportion of correct placements of the fingers/thumbs, (ii) greater mean (SD) depth (27.2 [5.7] vs. 22.1 [4.6] mm; $p = 0.0008$), and (iii) less mean (SD) depth variability (6.7 [3.2]% vs. 9.0 [2.8]%; $p = 0.002$) compared to the 2-finger technique during chest compression [83, 84]. There has been one animal study comparing the 2-thumb technique and the 2-finger technique in 9.4 (SD 0.8) kg infant swine, which reported significantly higher systolic, diastolic, and mean arterial blood pressure and coronary perfusion pressure [85]. More recently, newer techniques of how to position the thumbs and fingers during chest compression have been described in manikin studies; however, further studies investigating the optimal thumbs and fingers position during chest compression are urgently needed to improve the newborn infants' short- and long-term outcome.

Oxygen during Chest Compression

Current neonatal resuscitation guidelines recommend increasing oxygen to 100% when chest compression is started [18]; however, the optimal/most effective oxygen concentration during chest compression remains unknown/controversial. While there are no human data, animal studies reported that 21% O_2 results in not significantly different time to ROSC, survival, and neurologic outcomes compared to 100% O_2 [18]. A recent meta-analysis of animal studies reported that the pooled analysis showed no significant difference in mortality rates for animals resuscitated with air versus 100% O_2 (risk ratio 1.04 [0.35, 3.08], $I^2 = 0\%$, $p = 0.94$) [86]. ROSC was also similar between groups with a mean difference of −3.8 (−29.7 to 22) s, $I^2 = 0\%$, $p = 0.77$ [86]. Most recently, 2 further studies compared 21% with 100% O_2 using a neonatal asphyxia piglet model. No difference in time to ROSC, survival, oxidative stress, and inflammation markers was found [87, 88]. While these studies suggest that 21% is not different to 100% O_2, no clinical studies have been reported and are urgently needed.

Chest Compression during Sustained Inflation

An alternative chest compression method is chest compression superimposed during sustained inflation

(CC + SI), which (i) reduced time to ROSC and (ii) improved survival, (iii) improved hemodynamics (carotid artery blood flow and pulmonary artery blood flow), and (iv) resulted in passive ventilation during chest compression and thereby increasing minute ventilation compared with 3:1 C:V ratio in asphyxiated newborn piglets [89]. In a small human pilot trial in preterm infants <32 weeks, the time to ROSC was significantly shorter in the CC + SI group compared to the 3:1 C:V group with mean (SD) 31 (9) versus 138 (72) s [90]. The SURV1VE trial currently compares whether CC + SI with 3:1 C:V improves short- and long-term outcomes in preterm >28 weeks and term newborns (ClinicalTrials.Gov Trial NCT02858583) [91].

Vascular Access

Current neonatal resuscitation guidelines recommend to establish an intravenous access as soon as possible to administer epinephrine (adrenaline), fluids, or blood if needed [18, 19, 29]. The most common approach is to place an umbilical venous catheter ~5 cm into the umbilical vein [18, 19, 29]. This procedure could take several minutes, especially when the equipment is not prepared or performed by an inexperienced healthcare provider [92, 93]. Alternatively, a peripheral intravenous access or an intraosseous (IO) access could be established [1, 19, 94, 95]. Simulation studies reported that IO insertion was faster compared to umbilical venous catheter insertion [96]. Inserting a needle into the (tibial) bone allows a quick drug administration to the IO blood vessel system even during compromised circulation and shock. Cadaveric studies reported that IO needle position (i.e., humerus and proximal tibia) is feasible with both a semiautomatic battery-driven drill and manually inserted needles [97, 98]. A recent systematic review identified observational and simulation studies but no randomized trials [96]. A total of 46 IO needle insertions in 41 neonates (mostly inserted in the proximal tibia), with a complication rate of 13–31% (e.g., malpositioned needles, displaced needles, extravasation, local infection, osteomyelitis, fracture, compartment syndrome, limb ischemia, and fat or air emboli), was described [96]. More recently, Mileder et al. [99] reported 12 additional cases of IO needle insertions using a battery-driven drill in newborn infants with a 50% success rate for the first and second attempt. No long-term complications were reported; however, minor short-term complications (i.e., paravasation and local soft tissue infection) in 33% of successful IO insertions were observed [99]. The 2020 ILCOR neonatal resuscitation guidelines stated that if umbilical venous access is not feasible, the IO route is a reasonable alternative for vascular access during newborn resuscitation. However, adverse effects including tibial fractures and extravasation of fluid and medications resulting in compartment syndrome and amputation are emphasized [1].

Most recently, direct puncture of the umbilical vein through Wharton's jelly using a 24-gauge cannula as an alternative method for drug administration was described [100]. A case series of 10 cases ($n = 4$ epinephrine during CPR and $n = 6$ premedication of intubation) was described, and the whole procedure from puncture to drug administration took 15–20 s. There is a lack of data, and clinical trials are urgently needed.

Epinephrine (Adrenaline)

Current neonatal resuscitation guidelines recommend 1:10,000 epinephrine given intravenously at a dose of 0.01–0.03 mg/kg [1]. Alternatively, endotracheal administration at a dosage of 0.05–0.1 mg/kg might be considered while intravenous access is established [29]. Epinephrine acts on α- and β-receptors resulting in (i) increased coronary artery perfusion pressure via peripheral vasoconstriction, (ii) improved blood flow to the myocardium, and (iii) restored depleted energy substrates, thus improving myocardial contractility and viability. However, epinephrine also increases myocardial oxygen demand and respiratory and metabolic acidosis, a common occurrence during neonatal asphyxia [101]. A recent systematic review included 117 term and preterm infants receiving epinephrine in the DR and reported similar outcomes for death at hospital discharge (RR [95% CI] 1.03 [0.62–1.71]) or failure to achieve ROSC, time to ROSC, or proportion receiving additional epinephrine between intravenous and endotracheal epinephrine [102]. These data suggest that endotracheal and intravenous epinephrine results in similar survival and other outcomes. However, in animal studies, researchers continue to suggest benefit of intravenous administration using currently recommended doses. Human clinical trials are urgently needed.

Nonvigorous Infants and Meconium-Stained Amniotic Fluid

Meconium-stained amniotic fluid occurs in up to 15% of deliveries, 10–20% of these infants are born nonvigorous [103, 104], and 5–10% of these infants will develop meconium aspiration syndrome (MAS) [105, 106]. In

2015, the neonatal resuscitation guidelines changed their recommendation to emphasis not routinely suction in nonvigorous meconium-stained amniotic fluid infants [71]. Several studies compared outcomes before and after guideline changes and reported less neonatal intensive care unit admissions, less infants receiving tracheal suctioning, and no increase in severity of MAS or severe respiratory distress or other important neonatal outcomes [107–109]. Noteworthy, Kalra et al. [108] reported a similar prevalence of HIE and pneumothorax while Edwards et al. [107] reported an increased incidence. While Chiruvolu et al. [103] reported that a significantly higher proportion of nonvigorous infants with meconium-stained amniotic fluid were admitted with respiratory distress and respiratory support.

Recent meta-analyses included 581 nonvigorous infants with meconium-stained amniotic fluid and reported no difference in neonatal mortality, incidence of MAS and HIE, need for DR interventions, respiratory support, or hospital stay between suctioning below the vocal cord and no suctioning [110, 111]. These data suggest that there is no clear evidence of benefits of initial endotracheal intubation and tracheal suction in meconium-stained amniotic fluid; however, if there is airway obstruction due to thick viscous, meconium suctioning is often a clinical decision [17].

Temperature Management

Current neonatal resuscitation guidelines recommend maintaining body temperature of nonasphyxiated newborn infants between 36.5 and 37.5°C after delivery through admission and stabilization [19, 29, 72]. In infants with HIE, therapeutic hypothermia should be initiated within the first 6 h after birth [112]. Both active and passive cooling are feasible and safe to achieve a target body temperature of 33–34°C in asphyxiated term born infants >36 weeks' gestational age [113]. Asphyxiated newborn infants have impaired thermoregulation due to reduced oxygen consumption and energy production, a high surface area, and a wet and thin skin and lose temperature at a higher rate than nonasphyxiated infants. Infants with potentially higher degree of brain injury cool faster, as their natural protective mechanisms are inhibited [114, 115]. Initiating cooling sooner might prevent worsening of brain tissue injury; therefore, passive cooling should be started after the initial stabilization or during neonatal transport [116]. Especially in community hospitals or remote/rural areas, passive cooling is a good alternative to initiate cooling as early as possible. Several studies reported that infants passively cooled during transport achieved target temperature significantly faster compared to infants who were not passively cooled [117, 118]. However, passive cooling during transport resulted in ~1/3 of infants in overcooling, in particular in infants with mostly severe HIE [118, 119]. Overcooling can be avoided by using a servo-regulated cooling device (cooling blanket and rectal/esophageal temperature probe) during neonatal transport. A randomized controlled trial demonstrated that the mean time to reach target temperature with using a servo-regulated cooling device compared to either passively and/or actively (ice or gel packs) cooling was 44 min [120]. Thus, if servo-regulated cooling is initiated soon after arrival of the transport team in the birth hospital, many infants will achieve target temperature prior to departure from the birth hospital [120]. However, there is neither evidence nor clear recommendation how to process with body temperature of asphyxiated newborn infants with suspected HIE during neonatal resuscitation. The 2020 ILCOR neonatal resuscitation guidelines suggest treatment should be consistent with the protocols used in the randomized clinical trials [1]. This includes active cooling with ice packs [121]; however, caution is required when using this approach as it increases the risk for overcooling.

Neonatal Resuscitation in Resource-Limited versus Resource-Replete Environments

Of the approximately 2.6 million newborn infants who die annually, 98% occur in resource-limited environments, and 50–70% of neonatal deaths occur on the first day after birth [122]. Neonatal mortality is about 50–55 times higher in low- and middle-income countries compared to high-income countries due to mother's health (i.e., nutritional and infection status), limited resources, and lack of trained birth attendants or failure to provide adequate basic neonatal resuscitation at birth [123, 124].

Birth asphyxia is defined differentially in resource-limited and resource-replete environments [125]. However, in resource-limited environments, it is usually defined as a failure to initiate or sustain spontaneous breathing at birth and in some circumstances includes a 1-min Apgar score <7; in resource-replete environments, it is a biochemical definition (pH <7.00 and base deficit ≤−12 mmol/L), related to impaired gas exchange (leading to organ failure including HIE), due to interruption of placental blood flow, with progressive hypoxemia, hyper-

Table 2. Neonatal resuscitation of asphyxiated term infants in resource-limited versus resource-replete environments

	Limited resources	Replete resources
Cord clamping	Delayed cord clamping [120]	Immediate cord clamping to initiate resuscitation measures [18]
Basic steps of neonatal resuscitation	Dry thoroughly, keep warm, clear airway if needed, stimulate [120]	Dry thoroughly, keep warm, clear airway if needed, stimulate [18]
HR assessment	Auscultation if a stethoscope is available, if not cord palpation [121]	Pulse oximetry or ECG [18], stethoscope before PO, or ECG signals [2]
Meconium-stained amniotic fluid	Drying and stimulation before suctioning, if needed [120]	Emphasize initiating ventilation in nonvigorous infants, suctioning if airways are obstructed [19]
Indication to provide respiratory support	Apneic infants [120]	Apneic infants or/and HR <100 beats/min [18]
Respiratory support	Early continuous bag-mask ventilation [120] or using an LMA as alternative [63]	Mask ventilation using a manual ventilation device and escalate (intubation) if needed [18]
Supplemental oxygen	Room air [122]	Start with room air and titrate supplemental oxygen according to preductal oxygen saturation targets [18]
Cardiocirculatory support	No CC, no drugs such as epinephrine [114]	If the HR remains <60/min despite adequate ventilation, CC should be started and epinephrine administrated [18]
Temperature management	Swaddle in clean clothes or if available use clean food-grade plastic bag and swaddle [18, 120]	No clear recommendations, ILCOR suggest active cooling consider passive cooling [104]
Therapeutic hypothermia	Should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care [18]	Should be initiated according to strict criteria within 6 h after birth targeting a body temperature of 33–34°C [18]
Discontinuation of resuscitation	Stop assisted ventilation in babies with no spontaneous breathing despite presence of HR or Apgar score of 1–3 at 20 min or more [18]	Can be stopped if the neonate does not respond to continuous and adequate interventions around 20 min after birth. Consider individual decision-making [1]
Training strategies for healthcare providers	Low-dose, high-frequency practice, participation on programs such as "helping babies breathe" [120, 123]	Recurrent simulation and video-taping training, considered more frequently than once per year [18, 19]

ECG, electrocardiogram; HR, heart rate; CC, chest compressions; LMA, laryngeal mask airway.

capnia, and acidosis analyzing cord umbilical arterial blood after delivery of the newborn [125, 126].

To improve the outcome of newborn infants born in limited resource settings, the Global Implementation Task Force of the American Academy of Pediatrics developed together with other partners the "Helping Babies Breathe" training in 2010, a simulation-based training method designed to train healthcare providers in limited resource settings in neonatal resuscitation and care [127]. Implementing this training and resuscitation method is a simple and low-cost intervention that reduces intrapartum-related stillbirths and early neonatal mortality [127]. This systematic review showed moderate evidence for a decrease in intrapartum-related stillbirth and 1-day neonatal mortality rate after implementing the "Helping Babies Breathe" training and resuscitation method [127]. Table 2 gives an overview about the differences of recommendations regarding neonatal resuscitation in limited versus replete resource settings.

Discontinuation of Resuscitation

The current neonatal resuscitation guidelines [1] state that a reasonable timeframe to consider before ending resuscitation "is around" 20 min after birth. Recently, the Neonatal Life Support Task Force reported that 40% of infants with ongoing need for CPR at 10 min after birth survived with 11% surviving without moderate or severe impairment [128]. However, all included studies had high risk of bias, considering contextual factors such as gestational age, presence of congenital anomalies, or adequacy of resuscitative interventions performed. These data suggest that a uniform time interval or duration of CPR after birth will not be applicable [128]. The most recent guidelines suggesting to end resuscitation "around 20 min after birth" is a good approach for the patient, the parents, and the providers [1, 41].

Conclusion

DR management must be steadily evaluated, investigated, and trained to improve resuscitation of asphyxiated newborn infants. Current neonatal resuscitation guidelines often focus on preterm infants, not recommending different approaches for asphyxiated term born infants. Hence, strong efforts must be undertaken to perform studies of high quality in the DR to further improve neonatal resuscitation and outcome of one of the sickest groups of newborn infants.

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