SPECIAL ARTICLE

Neonatal resuscitation: An update

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ABSTRACT

International guidelines on neonatal resuscitation were published in 2010 based on the best available evidence. While many of these guidelines remain unchanged, subtle refinements have evolved with recent evidence. The aim of this review is to distill these recommendations, to provide updates where appropriate, and to condense them into a framework that is useful for the clinician. Birth depression is a common event, caused by both maternal and neonatal conditions. Prompt initiation of the most appropriate support is essential for achieving best outcomes. While ventilation of the small airways is the most important intervention in the neonatal resuscitation algorithm, progression to the next step is based on the simultaneous assessment of both heart rate and respirations. Serial clinical assessment of the response to interventions is fundamental to a successful resuscitation. Pulse oximetry should be used for assessing oxygenation when resuscitation is required. And generally speaking, term and near-term infants should be resuscitated using room air, while preterm infants should be resuscitated with the lowest concentration of oxygen needed to maintain normal oxygen saturations. Decisions regarding respiratory support should be individualized, but the lowest peak inspiratory pressure needed to achieve clinical improvement is advocated in neonatal resuscitation. The use of end-expiratory pressure reduces the need for invasive respiratory support, and support of spontaneous respirations with continuous positive airway pressure (CPAP) has been shown to result in improved long-term outcomes in preterm, but not term infants. Finally, circulatory support is rarely indicated in neonatal resuscitation scenarios, but is recommended in circumstances of presumed volume loss, persistent or prolonged bradycardia, or a persistent, suboptimal response to resuscitative efforts.

Key words: Infant mortality; Perinatal death; Resuscitation; Continuous Positive Airway Pressure; Infant, newborn; Respiration, artificial; Airway management; Pulmonary gas exchange; Positive end expiratory pressure

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INTRODUCTION

Approximately one quarter of all neonatal deaths are caused by birth asphyxia, and it is estimated that 10% of neonates require some form of resuscitation such as the application of CPAP or bag-valve-mask ventilation, while 1% require more vigorous efforts including ongoing mechanical ventilation, chest compressions or the administration of vasoactive medications. Effective and timely resuscitation during the newborn period can prevent a large proportion of these deaths. While the basic tenets of resuscitation (ABC's or airway, breathing, and resuscitation) remain unchanged, subtle refinements and modifications of resuscitative techniques have been suggested based on ongoing clinical and animal studies. The following manuscript will review the normal physiologic transition from fetal to neonatal existence and outline the basic principles of resuscitation as they apply to neonates immediately following delivery. We will emphasize airway management, early respiratory care, and cardiovascular resuscitation, but will also discuss

important aspects of care in the post-resuscitation phase of management, sometimes referred to as the "Golden Hour" of care.

PREPARATION

Anticipation of high-risk scenarios and preparedness are essential for an effective neonatal resuscitation. Every delivery should be attended by at least one health care professional whose only responsibility is the care of the neonate and who is capable of initiating resuscitative efforts including effective airway management and bag-valve-mask ventilation. Furthermore, either this person or someone who is immediately available should have the skills required to perform a complete resuscitation including obtaining vascular access. When the need for resuscitation is anticipated, additional personnel should be present in the delivery suite prior to the birth of the neonate. These situations may include persistent decelerations on fetal heart tone monitoring, infants with known critical congenital heart disease, various congenital anomalies, or significant prematurity. After the team arrives, the needed equipment should be prepared in anticipation of the delivery to allow for a timely resuscitation (Table 1).

Table 1: Suggested equipment for neonatal resuscitation

1.	Radiant warmer (turned on to warm the bed)
2.	Resuscitation bag and mask
3.	Source for free flow oxygen with blender to allow delivery of various concentrations from 21% to 100%.
4.	Ready access to surfactant preparations as indicated
5.	Devices for the administration of continuous positive airway pressure (CPAP)
6.	Laryngoscopes
7.	Endotracheal tube and stylet
8.	Oral airways
9.	Suction
10.	Supplies for vascular access including periphera cannula, umbilical catheters, and intraosseous needle
11.	Resuscitation medications (atropine, epinephrine, naloxone, glucose, neuromuscular blocking agent)
12.	Analgesic agents (fentanyl)
13.	Monitoring devices including pulse oximetry, blood pressure cuffs, electrocardiogram.

TRANSITION FROM FETAL TO NEONATAL PHYSIOLOGY

Many physiologic changes accompany the transition from intrauterine to extrauterine life. The transition from the fetal (in utero) to neonatal (extrauterine) life involves a series of significant physiologic changes occurring shortly after birth. Any factor that interrupts or delays this process can have significant deleterious impact on physiologic function resulting in morbidity and even mortality. While in utero, prior to delivery, the fetus is dependent on the placenta to accomplish the normal physiologic functions of gas exchange (oxygen uptake and carbon dioxide removal) and nutrient delivery. Any factor that affects the development, attachment or function of the placenta can result in significant in utero disturbances including growth retardation, premature delivery or even death. As the placenta and not the lungs are responsible for gas exchange, the vascular patterns in utero are quite different from ex utero life. The low vascular resistance of the placenta and the high resistance of the pulmonary circulation result in right-to-left shunting of the fetal circulation. Given its low vascular resistance, the placenta receives 40-50% of the fetal cardiac output while less than 10% traverses the pulmonary circulation. Blood is carried to the placenta via two umbilical arteries and returned through a single umbilical vein. The right-to-left shunting that occurs in utero serves to bypass the pulmonary vascular and limit pulmonary blood flow. The two conduits that result in right-to-left shunting include the foramen ovale which shunts blood from the right to left atrium and the ductus arteriosus which shunts blood from the pulmonary artery to the aorta.

Oxygenated blood returning from the placenta flows through the umbilical vein, the majority flowing through the ductus venosus returning the right atrium via the inferior vena cava. The majority of this oxygenated blood is then shunted across the foramen ovale into the left atrium to eventually eject through the aorta to perfuse the head and upper body. The less well oxygenated blood returning into the superior vena cava crosses the tricuspid valve into the right ventricle and then into the pulmonary artery and across the ductus arteriosus to the supply the lower extremity and more importantly the umbilical arteries. As such, this deoxygenated blood flows to the placenta to receive oxygen and release carbon dioxide. Given the admixture of blood that occurs in utero, the partial pressure of oxygen in fetal blood is approximately 40 mmHg, being highest (50-60 mmHg) in the umbilical vein. Despite the relative hypoxemia of fetal blood, oxygen delivery to the tissues is maintained by:

1. Fetal hemoglobin. Fetal hemoglobin consists of two α and two γ chains (compared to β chains in adult hemoglobin. This different hemoglobin

composition results in altered binding of 2,3 DPG (diphosphoglycerate) and a left-ward shift of the oxy-hemoglobin dissociation curve and hence a lower P50 (partial pressure of oxygen at which hemoglobin is 50% saturated). This means that the hemoglobin has a higher affinity for oxygen, which facilitates saturation during a lower PaO_2.

2. Decreased fetal oxygen consumption. In utero existence has a lower metabolic demand and hence lower oxygen needs. Most physiologic functions are reduced including respiratory effort, gastrointestinal function, and renal tubular function. The oxygen needs are further decreased as the fetus does not have to maintain normothermia, a process provided by the mother.
3. Increased effective cardiac output in utero compared to ex utero with differential blood flow. As noted above, the vital organs (liver, heart, and brain) receive blood with a relatively high degree of oxygen saturation.

Shortly after delivery with the initiation of the first breath, the transition to neonatal life begins. The most immediate adaptations are the clearance of amniotic fluid, initiation of breathing, and the transition from fetal to adult circulation. The transition includes alveolar fluid clearance, lung expansion, and circulatory changes with increases in pulmonary perfusion and systemic pressure, and closure of the right-to-left shunts of the fetal circulation. There is an increase in systemic vascular resistance associated with clamping of the umbilical cord. Increased oxygen tension resulting from the first breath leads to increased endogenous prostaglandin levels, which typically leads to closure of the ductus arteriosus and a steady decrease in pulmonary vascular resistance. Complications of the pregnancy and/or delivery may alter the normal physiologic transition, increasing the risk that these important physiologic changes are interrupted or modified. The preterm newborn is at even greater risk. Immature thermoregulatory and adaptive systems, poor/incomplete glycemic stores, and the fragile preterm brain further increase the risk of a poor outcome.[1]

Complications of the transition to neonatal physiology:

The absence of spontaneous respirations (apnea) is the first clinical sign that a newborn is compromised in the perinatal period. Perinatal stress results in a period of rapid breathing followed by a period of primary apnea (or gasping respirations).[2] Primary apnea is common, and requires only minimal intervention such as drying or stimulation to reverse the process. The heart rate tends to decrease at or around the time that primary apnea is noted, but blood pressure is usually maintained during this period. Secondary apnea, on the other hand, occurs when cardiorespiratory compromise is prolonged or goes unmitigated for an extended period of time. Secondary apnea, unlike primary apnea, requires more than drying and stimulation to reverse the process.[2] Moreover, if secondary apnea is prolonged, blood pressure and perfusion will be further compromised, and the longer the infant remains in secondary apnea, the longer it will take for spontaneous respirations to return.[2]

As of 2010, it was estimated that birth depression occurred in approximately 1.15 million newborns worldwide (8.5 per 1000 live births) with an estimated 25% (287,000) risk of mortality in infants with neonatal encephalopathy.[3] Approximately 63% survived with mild neurodevelopmental impairment while 11% had moderate to severe impairment at follow-up.[3] Birth depression can be caused by a variety of clinical conditions including placental abruption, placental infarction, uteroplacental insufficiency, shoulder dystocia, or abnormalities of fetal perfusion (nuchal cord, knotted cord). The high risk delivery presents a number of challenges. There is frequently limited time for preparation (chaotic environment), pregnancy information may not available at the time of delivery (unclear physiology), and clinical decisions must be made quickly in many cases. Regardless of the circumstances, management of the depressed infant can be challenging, and a lack of preparedness can impact the outcome. The emphasis here is on delivery room management, but we will also discuss early post-resuscitation management, as suboptimal care in the "Golden Hour" has been associated with poor outcomes.[4-9]

RESUSCITATION ALGORITHM AND EARLY POST-RESUSCITATION CARE

The International Liaison Committee on Resuscitation (ILCOR), the American Academy of Pediatrics (AAP), and the American Heart Association (AHA) have published recommendations on neonatal resuscitation derived from the best available evidence.[10-12] The following is intended to distill the available evidence, to provide updates where appropriate, and to place these recommendations into a framework that is useful for clinicians.

Initial Steps in the resuscitation algorithm: Infants born at term, that are either breathing or crying and have good tone, should simply be dried and kept warm.[2] These infants are usually placed on the mother's chest to enhance bonding and thermoregulation. This process is sometimes referred to as a "routine stabilization". However, if the infant is preterm, not breathing or crying, or has poor tone, then the infant's heart rate, respiratory effort, and color should be assessed immediately. If the heart rate, respirations, or color are suboptimal, then the "initial steps" of neonatal resuscitation are indicated. These initial steps include:

1. drying the infant with mild stimulation
2. providing warmth
3. suctioning the airway, as indicated
4. stimulating the infant to breathe.

Next steps in the resuscitation algorithm: Published guidelines suggest that progression to the "next step" in the resuscitation algorithm should be based on the simultaneous assessment of heart rate and respirations, and the "next step" should be initiated only after the preceding step has been accomplished.[13] If the "initial steps" of a neonatal resuscitation are not met with clinical improvement, some form of intervention is required. An effective resuscitation is indicated first by an improvement in heart rate and respiratory effort, and then by an improvement in color and tone. Since an increase in heart rate is the most sensitive indicator of an adequate resuscitation, it is the primary determinant of the efficacy of the resuscitation, and is best assessed by auscultation.[13-15]

Generally speaking, ventilation of the small airways is the most important "next step" in the neonatal resuscitation algorithm. For the preterm infant with adequate respiratory drive, CPAP may be sufficient if the heart rate is > 100 beats/minute (bpm). However, positive pressure ventilation (PPV) is indicated if the heart rate is < 100 bpm or if apnea or gasping is noted. If, despite effective PPV, the heart rate remains < 60 bpm, then chest compressions are indicated. If there is no improvement in clinical status despite effective, coordinated PPV and chest compressions, then administration of epinephrine is indicated. The vast majority of infants with a heart rate < 100 bpm will respond to PPV. In some cases, supplemental (blow-by) oxygen may be sufficient, e.g. term infants with a heart rate > 100 bpm with adequate respiratory drive. Determination of the most appropriate intervention should be made within 60 seconds of delivery.[11]

ASSESSING THE RESPONSE TO RESUSCITATIVE EFFORTS:

Serial clinical assessment of the response to interventions, at 30 second intervals, is currently recommended. While the most appropriate interval may be questioned, *periodic clinical assessment* of the infants status is among the most important fundamentals of a successful neonatal resuscitation.[11,16] After an initial period of ventilation, the heart rate and respiratory status should be assessed. If resuscitative efforts are successful, and spontaneous respirations are present, then PPV should be discontinued. If, on the other hand, the heart rate remains less than 100 bpm, PPV should be continued, and an alternative airway should be considered. If spontaneous resuscitations are absent, PPV should be continued and an alternative airway should be considered, even if the heart rate has improved. Once endotracheal intubation has occurred, proper tube placement should be verified with end-tidal capnography, as dislodgment is common in high-risk scenarios and simple auscultation may be misleading.[6] However, the presence of end-tidal carbon dioxide is dependent on effective pulmonary blood flow; hence, end-tidal carbon dioxide may be absent during cardiac arrest or with poor cardiac output. If, despite effective PPV, the heart rate remains < 60 bpm, PPV should be continued and chest compressions should be initiated (see below for discussion of cardiovascular resuscitation).[2]

While color (cyanosis) is frequently used to guide decision-making, clinical studies have shown that it is unreliable in predicting the level of oxygenation, even among experienced clinicians.[17,18] For this reason, a pulse oximetry probe should be available for all deliveries, and should be applied for all infants requiring resuscitation.[6,13,19] As a general rule, pulse oximetry should be used when resuscitation is anticipated, when more than a few breaths of PPV is offered, when cyanosis is persistent, and when supplementary oxygen is administered.[11] Although obtaining a reliable pulse oximetry signal is sometimes problematic, there is evidence that a good oximetry signal is best obtained by performing the following in sequence: (1) turn the oximeter "on", (2) place the oximetry probe on the infant, and finally (3) connect the oximetry lead to the oximetry device.[17]

SUCTIONING THE AIRWAY

Historically, it was standard practice to suction the airways of newborn infants, regardless of the

quality or quantity of secretions noted. However, current evidence-based medicine provides no support for this approach.[11] Suctioning the airway is not benign as it may cause cardiorespiratory depression, alterations in cerebral blood flow, and increased intracranial pressure.[20-22] Given the absence of proven benefit, and the possibility of harm, current guidelines now suggest that airway suction be avoided unless there is clinical evidence of an airway obstruction affecting ventilation.[11]

Infants born through meconium-stained amniotic fluids, however, remain at risk for complications related to meconium aspiration syndrome (MAS), and a variety of strategies have been proposed to minimize this risk with no evidence of improvement. In two large multi-center, randomized trials, totaling over 4000 infants, suctioning of non-vigorous infants and suctioning at the perineum failed to reduce the incidence of meconium aspiration syndrome.[23,24] In short, tracheal suctioning does not appear to reduce the incidence of MAS or mortality. However, the combined evidence neither supports nor refutes routine suctioning of tracheal secretions in depressed infants born through meconium-stained fluids, and for this reason, a change in clinical practice is not recommended.[11,13]

TROUBLESHOOTING

The goal in applying positive pressure is to improve pulmonary gas exchange by establishing functional residual capacity and achieving adequate minute ventilation. When performed correctly, PPV usually results in an immediate improvement in heart rate and respirations. However, if improvement is not appreciated with initial resuscitative efforts, the troubleshooting algorithm advocated by NRP, and best remembered by the acronym "MR SOPA", is a helpful aid for rapid decision-making.[2] The acronym describes the suggested progression of step-wise interventions for infants not responding to initial resuscitative efforts:

1. Adjust the ***m***ask (seal)
2. ***r***eposition the head (sniffing position)
3. ***s***uction the airway (obstruction)
4. ***o***pen the airway (jaw thrust), and
5. increase the ***p***ressure, as indicated.
6. Finally, if no improvement is noted with the preceding steps, an ***a***lternative airway is indicated (endotracheal tube, laryngeal mask airway).

Effective PPV requires adequate pressure to achieve appropriate tidal volumes and minute ventilation. In general, peak inspiratory pressures (PIPs) less than 30 cmH_2O are usually sufficient for term infants while a PIP less than 25 cmH_2O is usually sufficient for preterm infants. Nonetheless, care should be individualized, and an inadequate response to initial efforts suggests the need for troubleshooting (MR SOPA), which may indicate the need for an increase in pressure (PIP). Preterm infants have immature lungs that are less compliant and more difficult to ventilate, but also more vulnerable to injury (volutrauma, barotrauma, and/or atelectotrauma).[25,26] Lung protection should begin with the first positive pressure breaths, as excessive tidal ventilation is associated with lung injury with as few as 6 positive pressure breaths.[27,28] Therefore, the best available evidence indicates that the minimum PIP required to achieve an improvement in heart rate is desired.[1,4]

USE OF SUPPLEMENTAL OXYGEN:

The oxyhemoglobin saturation level (SpO_2) in healthy infants is typically less than 80% for several minutes following birth. Recent guidelines suggest that an SpO_2 of 80% and 85% are acceptable at 5 and 10 minutes, respectively. There is also a growing body of evidence in human and animal studies that excessive oxygen administration can do harm.[29] Oxygen, in high concentrations, is associated with both oxidative stress and tissue injury in animal models of hyperoxia following birth asphyxia.[30,31] Moreover, resuscitation with 100% oxygen in infants with hypoxic ischemic encephalopathy is associated with increased brain injury, and may mitigate the beneficial effects of therapeutic hypothermia.[32,33]

In an updated meta-analysis, neonatal mortality was higher in depressed term and late-preterm infants exposed to 100% oxygen during resuscitation.[29] In studies of preterm infants requiring resuscitation, including a recently published meta-analysis, days on the ventilator, days on CPAP, rates of BPD, and mortality were improved in infants exposed to lower fractions of inspired oxygen at resuscitation (21-30%).[31,34,35] Therefore, term and near-term infants without evidence of lung disease should be resuscitated using room air, and preterm infants should be resuscitated with the lowest concentration of oxygen needed to maintain normal oxygen saturations. If, despite effective ventilation, oxygenation saturations remain unacceptably low or there is evidence of lung disease, the use of higher oxygen concentrations is appropriate, regardless of the gestational age.

USE OF END-EXPIRATORY PRESSURE:

Clearance of lung fluid and lung aeration are among the most important early physiologic adaptations in the transition to extrauterine life.[36] Current evidence supports the use of positive end expiratory pressure (PEEP) in preterm infants for stabilization and resuscitation.[26] The mechanisms by which clinical improvement is noted are multifactorial, but include: increases in lung volume and pulmonary surface area, and improvements in lung compliance. Secondary effects include reducing alveolar collapse at end-expiration, and possibly conserving surfactant.[25] While the evidence supporting its use in preterm newborns is substantial, there is limited evidence to support the use of CPAP in term infants.[13] CPAP reduces the need for endotracheal intubation, mechanical ventilation and surfactant administration in preterm infants, but also increases the risk of pneumothorax.[37] It should be noted that CPAP levels > 8 cmH_2O have been associated with both restricted pulmonary blood flow and pneumothorax.[38,39] Therefore, while the use of CPAP is a proven strategy for resuscitation of preterm infants, end-expiratory pressures > 8 cmH_2O should generally be avoided due to potential complications. CPAP, especially at higher pressures, should be used with caution in term newborns until more evidence is available.[11,13]

CPAP VS. INTUBATION AND SURFACTANT ADMINISTRATION:

Previous evidence-based practice guidelines recommended administration of surfactant at or soon after birth in preterm infants with Respiratory Distress Syndrome (RDS). In early randomized trials, prophylactic surfactant administration has been shown to decrease mortality, bronchopulmonary dysplasia (BPD), and the incidence of pneumothorax.[40,41] In subsequent trials, early selective surfactant, when compared to delayed selective surfactant, improved these same outcomes.[41] A modification of the traditional practice of prophylactic endotracheal intubation and surfactant administration (with subsequent mechanical ventilation) is the so called "INSURE" method (Intubate, SURfactant, and Rapid Extubation).[42] A number of clinical trials have included variations of this method. Overall, the literature suggests that if endotracheal intubation and surfactant administration are indicated the INSURE method is favored over both early prophylactic surfactant with subsequent mechanical ventilation and selective surfactant administration with subsequent mechanical ventilation.[42]

As data have accumulated from these clinical trials, it has become apparent that infants stabilized on CPAP (without prophylactic endotracheal intubation and surfactant administration) have reduced rates of mechanical ventilation and surfactant usage.[26,37] Approximately 50% of infants stabilized on CPAP still required endotracheal intubation. However, infants stabilized on CPAP had fewer days on mechanical ventilation, and fewer required oxygen at 28 days of life.[37] A meta-analysis of eleven clinical trials comparing prophylactic surfactant administration compared to selective surfactant administration for infants with established RDS demonstrated no difference in the composite outcome death or BPD.[42,43] Analysis of studies that permitted stabilization on CPAP revealed decreased rates of death and BPD among infants that were stabilized on CPAP. When all eleven studies were evaluated together, the benefits of prophylactic surfactant administration could no longer be demonstrated.[43] Our interpretation of the literature suggests that stabilization of premature infants on CPAP should now be considered the standard of care. However, infants that meet criteria for selective endotracheal intubation and surfactant administration should receive such therapy as soon as possible with rapid tracheal extubation to CPAP (INSURE method).

INDICATIONS FOR ENDOTRACHEAL INTUBATION:

Generally speaking, the indications for endotracheal intubation remain unchanged including failure to oxygenate, failure to ventilate, failure to maintain an airway, and/or central apnea. The challenge, however, is application of the available evidence, as there is not one "gold standard" threshold for when to secure an alternative airway. Some clinicians provide endotracheal intubation for high oxygen requirements on CPAP, while others use work of breathing or laboratory criteria (hypoxemia or hypercapnia). While indications for endotracheal intubation in neonates remain controversial, there is less controversy about proper techniques. While previous NRP guidelines suggested endotracheal intubation attempts should be limited to 20 seconds, recent data suggests that modifying the expectation to 30 seconds resulted in a substantial increase in the frequency of success and an improvement in arterial oxygen saturations.[44] Endotracheal tube placement should be confirmed by capnography, as studies have demonstrated that end-tidal CO_2 detection confirms endotracheal intubation more

rapidly and accurately than clinical assessment alone.[45] The latter is especially true in preterm neonates where auscultation can be misleading and inaccurate._

RESPIRATORY DEVICES USED IN NEONATAL RESUSCITATION:

Three respiratory devices are commonly used in neonatal resuscitation: the self-inflating Ambu-bag (bag-valve-mask), which requires no gas source; the flow-inflating resuscitation (anesthesia) bag, which requires a pressurized gas source; and the T-piece resuscitator, which also requires a pressurized gas source. Self-inflating bags are unable to provide PEEP, and do not permit adjustments in inspiratory time. The flow-inflating (anesthesia) reservoir bag, on the other hand, when used properly, permits use of both PEEP and variable inspiratory times. The T-piece resuscitator, which provides positive pressure by periodic occlusion of a release valve on the apparatus, is gaining popularity due to its ease of use and the consistent delivery of pressure to the airway.[46] In a recent study, using a neonatal lung model, a mechanically-operated self-inflating bag was compared to a manually-operated T-piece resuscitator at various respiratory rates (40, 60, and 80 breaths per minute). With increasing rates, leak-dependent decreases in pressure (PIP and PEEP) were significantly greater for the self-inflating bag than for the T-piece resuscitator.[47] While we view the T-piece resuscitator as the most reliable means of delivering consistent tidal ventilation, the most desirable resuscitation equipment is the one with which the provider is most comfortable and capable.[6]

CIRCULATORY AND HEMODYNAMIC SUPPORT:

Cardiac output is affected by a number of clinical conditions that vary with the infant's physiology (postnatal transition to extrauterine life) and the approach to resuscitation. Circulatory support is rarely needed in neonatal resuscitation scenarios, as less than 1 in 1000 newborns require the use of chest compressions or the administration epinephrine.[6] As a rule, resuscitative medications are rarely indicated. The 2010 ILCOR guidelines for newborn resuscitation state that: "Drugs are rarely indicated in resuscitation of the newly born infant. Bradycardia in the newborn infant is usually caused by inadequate lung inflation or profound hypoxia, and establishing adequate ventilation is the most important step to correct it."[11] Nonetheless, chest compressions should be initiated if, after 30 seconds of *effective* PPV, the heart rate remains less than 60 beats/minute.[2,11] There is currently no evidence from human, animal, or manikin studies to suggest a change in the current standard compression to ventilation ratio of 3:1.[48] Chest compressions should be delivered using the two-thumb encircling method, over the lower 1/3rd of the chest (sternum) at a depth of at least 1/3rd of the anterior-posterior diameter.[11,48,49]

Guidelines suggest that epinephrine should be administered if, after 30 seconds of *effective* PPV, followed by 30 seconds of coordinated chest compressions and PPV, the heart rate remains less than 60 bpm.[50,51] This recommendation is supported by animal studies demonstrating that the combination of chest compressions and ventilations is associated with better outcomes than those when either intervention is used alone.[52,53] Current guidelines suggest that epinephrine should be administered via the most readily available route (endotracheal or intravenous).[2] While epinephrine administered via the endotracheal tube may produce a return of spontaneous circulation, animal studies suggest that higher doses (0.05 – 0.1 mg/kg) are needed to achieve an equivalent response to that of IV administration (0.01 mg/kg).[54] If indicated, IV epinephrine should be administered at a dose of 0.01 mg/kg to 0.03 mg/kg. The concentration of epinephrine used most frequently in neonatal resuscitation is 1:10,000, equivalent to 0.1 mg/ml so that dosing for intravenous administration is 0.1 to 0.3 ml/kg. There is no role for higher doses of intravenous epinephrine during resuscitation. If intravenous access is unavailable, administration via the endotracheal tube is reasonable at a dose of 0.05 to 0.1 mg/kg (0.5–1 ml/kg of 1:10,000 epinephrine); higher doses should be avoided due to the potential for adverse physiologic effects.[13]

While adequate preload is required to support cardiac output, volume-resuscitation is rarely indicated in neonatal resuscitation scenarios except in those rare circumstances where neonatal blood loss has occurred.[55] It is estimated that only 1 in 12,000 newborns require volume resuscitation.[6] That said, volume resuscitation should be considered when blood loss is known or suspected (pallor, delayed capillary refill, weak pulses), or if the infant has not responded to other resuscitative efforts. Isotonic crystalloid or blood is recommended at a dose of 10 ml/kg. Repeated doses may be indicated in certain high-risk scenarios. We urge caution in the use of

volume expansion, especially in preterm infants, as there is an association between rapid volume expansion and intra-ventricular hemorrhage in this population.[56,57] Further, there is no evidence that transitional hypotension is associated with white matter damage, cerebral palsy, or functional developmental impairments at 2-year follow-up in preterm infants.[58-59]

The use of sodium bicarbonate ($NaHCO_3$) as a routine part of neonatal resuscitation is not evidence-based and is not recommended.[51] While $NaHCO_3$ administration has historically been used as a bridge to more advanced therapies, such as high-frequency ventilation or extra-corporeal membrane oxygenation (ECMO), the most recent clinical and animal data suggest little utility and potentially, substantial harm.[60] Both human and animal studies have shown that the carbon dioxide generated after the administration of sodium bicarbonate is detrimental to both myocardial and cerebral function.[61,62] Generally speaking, $NaHCO_3$ administration should only be considered in the very rare case of a compromised infant with profound/persistent bradycardia with presumed acidosis, who despite adequate ventilation and chest compressions, fails to respond to the previously discussed interventions in the resuscitation algorithm. However, even in this specific case, there is little or no evidence of efficacy.[11] Whenever a decision is made to administer $NaHCO_3$, appropriate neonatal preparation (0.5 mEq/L) should be used to avoid adverse effects related to rapid administration of hyperosmolar fluids. If such preparation is not possible, standard strength solution (1 mEq/ml) can be diluted with preservative-free sterile water (not normal saline) to decrease its osmolarity.

Recent publications suggest that delayed cord clamping may be beneficial for healthy late-preterm and term newborns, as long as there is access to treatment modalities for hyperbilirubinemia.[63] Delayed cord clamping in preterm infants is associated with a reduced need for blood transfusion and lower rates of intraventricular hemorrhage.[64] However, delayed cord clamping may also delay critical resuscitative efforts. For this reason, the benefits do not appear to outweigh the risks for infants requiring resuscitation efforts. Although emerging evidence may further delineate its utility in premature infants, there is currently insufficient clinical data to support delayed cord clamping in infants that are either sick or require resuscitation.[65]

VASCULAR ACCESS:

Intravenous access is an important element of resuscitative efforts in critical scenarios, providing life-saving access to the circulation. While umbilical vein cannulation remains the preferred method of rapid IV access, if umbilical venous access becomes a challenge ad peripheral venous access cannot be attained, there is sufficient evidence that the intraosseous route is a reliable method of delivering crystalloid, blood, and medications to the circulation in neonates.[66,67] Generally speaking, and assuming reasonable efforts have been made to achieve peripheral and/or umbilical cord access to the circulation, delivery of needed resuscitation medications should not be delayed in efforts to avoid an intraosseous insertion. We would generally recommend this route over the endotracheal route for the administration of epinephrine and other resuscitative medications.

GLUCOSE HOMEOSTASIS:

Newborns with hypoglycemia are at increased risk of brain injury, especially following a hypoxic-ischemic insult.[68] On the other hand, there are no clear data to indicated that acutely elevated blood glucose levels are associated with harm in newborn infants.[69] While no specific target blood glucose has been identified, hypoglycemia should be avoided in the high-risk neonate.[11] Infants requiring resuscitative measures should be monitored for hypoglycemia. We would also suggesting obtaining intravenous access in at-risk infants to allow for early intervention. We suggest that serum blood glucose levels should be maintained at or above 50 mg/dL, especially those that have suffered a hypoxic-ischemic insult.[11] As with the administration of $NaCO_3$, hyperosmolar glucose solutions (D_{25} or D_{50}) should be avoided. Hypoglycemia should be treated with 1-2 ml/kg of 10% glucose in water ($D_{10}W$) followed by the administration of 4-6 mg/kg/minute of glucose containing intravenous fluids, with ongoing checks of serum glucose.

THERMOREGULATION:

Admission to the NICU for the evaluation and treatment of hypothermia is common in critically ill term and preterm infants. Forty-eight percent of preterm infants in the EPICURE Study were admitted to the NICU with a temperature < 36.5°C.[70] In a study of late preterm infants, only 51% of infants admitted to the newborn nursery had a body temperature within the normal range (36.5-37.5°C.[7] Thermoregulation is a critical aspect of

neonatal care, as hypothermia has been associated with alterations of cerebral and peripheral vascular tone, hypoglycemia, acid-base imbalance, hypoxia-ischemia, systemic hypotension, and mortality.[7] Preterm infants weighing less than 1500 grams should be stabilized in delivery rooms where the ambient temperature is maintained at ≥ 26 ºC and covered up to the neck (without drying) with a medical-grade, heat-resistant plastic wrap. They should be placed on an exothermic mattress and maintained under radiant heat until their temperature has been verified in the NICU.[71,72] Regardless of gestational age, all newborns should be stabilized in a thermoneutral environment, and maintained at core body temperature of 37.0 ± 0.5ºC.

The use of therapeutic hypothermia (whole-body or selective head-cooling) in term and near-term asphyxiated infants has been shown to decrease the risk of death or disability in infants with moderate to severe hypoxic-ischemic encephalopathy.[73,74] Thus, ILCOR has declared that there is now sufficient evidence to support the practice of therapeutic hypothermia for infants with clinical evidence of moderate to severe encephalopathy following events in the perinatal period that are believed to have contributed to the infant's neurologic depression.[11] We recommend stabilization and transport to a level III NICU with active clinical protocols for therapeutic hypothermia. Core temperatures should be reduced to 33.5□C within 6 hours of birth and laboratory studies should be monitored according to established protocols. Close neurodevelopmental follow-up after discharge is imperative.

CONCLUSION

Published studies from the NICHD reveal significant differences in outcomes among centers for all gestation ages.[75] These data suggest that differences in practice are likely responsible for differences in outcomes. Differences in outcomes have been linked with teamwork in the operating room, in Pediatric Residency training programs, and in Perinatal Service domains.[76,77] Therefore, anticipation of high-risk scenarios, planning and preparation, including use of briefings and debriefings before and after critical encounters can improve teamwork and outcomes. While each high-risk scenario will have its own challenges, this summary of the available evidence-based guidelines should be helpful for the clinician involved in neonatal resuscitation. As outlined above, resuscitation protocols should be tailored according to the clinical status and presentation of the neonate. Titrating the inspiratory fraction of oxygen to avoid oxidative stress and using non-invasive ventilation to reduce trauma to the lung are keys in ensuring best outcomes from pulmonary complications of the neonatal period. Developing systematized strategies to treat cardiovascular instability, provide cardiopulmonary resuscitation, avoid hypothermia, and achieve fluid imbalance and hypoglycemia are important means of minimizing the risks associated with high-risk deliveries. Together, these strategies can be used to improve the perioperative outcomes of all neonates.

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