

Guidelines for Perinatal Management of the Extremely Premature Infant During the First Week of Life

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PROVISIONAL BEST PRACTICE STATEMENT:

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While Intraventricular Hemorrhage (IVH) remains the most common cause of brain injury in pre-term infants, it is recognized that neurologic injury can be caused by a variety of insults including, but not limited to, white matter injury, inflammatory changes, infection, intermittent hypoxia, and nutritional deficiencies. For IVH, there is an inverse relationship between gestational age at birth and injury risk, with nearly all cases occurring in the first week of life and many within the first 24 hours of life. (1) Other causes of neurologic injury may be more insidious, and the infant is at risk throughout the NICU hospitalization. Prevention of preterm birth and extension of gestation is the ultimate strategy to reduce rates of neurologic injury in extremely premature infants. Several interventions exist to reduce the risk of adverse outcomes if preterm birth cannot be prevented. These guidelines will describe strategies in the antepartum period, during resuscitation and transition to extra-uterine life, and the early postnatal phase of care.

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“While the primary focus is reducing the risk of IVH, the guidance attempts to address all causes of adverse outcomes. Wherever possible, the available evidence in the literature was used to guide recommendations. When evidence is equivocal, recommendations are based on committee consensus opinion. Overall, consistent care with the implementation of guidelines and a multidisciplinary team approach is imperative for caring for extremely premature neonates. (2–4)”

While the primary focus is reducing the risk of IVH, the guidance attempts to address all causes of adverse outcomes. Wherever possible, the available evidence in the literature was used to guide recommendations. When evidence is equivocal, recommendations are based on committee consensus opinion. Overall, consistent care with the implementation of guidelines and a multidisciplinary team approach is imperative for caring for extremely premature neonates. (2–4)

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ANTENATAL CARE:

American College of Obstetricians and Gynecologists (ACOG) Interim Update, Oct 2017 (5), defined periviability as “newborns delivered near the limit of viability whose outcomes range from certain or near-certain death to likely survival with a high likelihood of serious morbidities.” The Joint Workshop of SMFM (Society for Maternal-Fetal Medicine), NICHD (National Institute of Child Health and Human Development), AAP (American Academy of Pediatrics) Section on Neonatal-Perinatal Medicine, and ACOG define perivable birth as 20+0/7 to 25+6/7 weeks gestational age (GA). (6) Doshi et al, published in 2022 on the survival of extremely

premature infants to discharge and secondary outcomes including, bronchopulmonary dysplasia, necrotizing enterocolitis stage ≥ 2 , periventricular leukomalacia, severe intraventricular hemorrhage, and severe retinopathy of prematurity.

Of the 71,854 infants born ≤ 24 weeks GA from 2009-2018, 34,251 (47.7%) survived < 1 day and were excluded from the study. Among 37,603 infants included in the study cohort, 48.1% were born at 24 weeks GA. Of these, survival to discharge increased from 58.3 to 65.9%. Survival to discharge for infants ≤ 23 weeks GA increased from 29.6% in 2009 to 41.7% in 2018. About 90% of infants born ≤ 23 weeks GA either died or had at least one major morbidity (BPD, severe NEC, severe neurological injury, and severe ROP) compared with 80% of infants born at 24 weeks GA.

“Communicate discussion and plan of care with obstetrics/maternal-fetal medicine (OB/MFM). Outcomes should be discussed with parents and OB/MFM to understand possible treatment options. The parents should receive the most accurate and up-to-date prognostic data to help them make decisions. Counseling should be individualized—avoid “always” or “never” as a part of the consult; care should be provided in steps, with frequent re-evaluation.”

Younge et al. reported on outcomes of 4,000 births between 2001–2011, at 22+0/7 to 23+6/7 weeks gestation, 64% died, and 16% were severely impaired. Among infants 22+0/7 to 22+6/7 weeks gestational age, death rates were 97–98%, with only 1% surviving without neurodevelopmental impairment. In those born at 24+0/7 to 24+6/7 weeks gestation, 55% of neonates survived, 32% without evidence of neurodevelopmental impairment at 18–22 months corrected gestational age (CGA).

Death, neurodevelopmental impairments, and adverse outcomes remain high in newborns born at periviable age despite improvements in care. Outcomes are better grouped with adjacent weeks—i.e., 22+6/7 week outcomes are closer to 23-week vs. 22-week outcomes, and 22+1 week outcomes are closer to 21-week versus 22-week outcomes.

Prenatal Periviable Counseling:

When possible, offer an antenatal consultation with neonatology for families anticipating the delivery of an extremely immature periviable infant. Document the consultation and recommendations in the mother’s electronic record. The attending neonatologist should be notified of a pending delivery of an infant in the periviable period and, ideally, personally attend the delivery.

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as a part of the consult; care should be provided in steps, with frequent re-evaluation.

NIH (National Institutes of Health) provides a website called [Extremely Preterm Birth Outcomes Tool](https://www.nichd.nih.gov/research/supported/EPBO) [https://www.nichd.nih.gov/research/supported/EPBO] with national data for survival and morbidity based on gestational age, gender, antenatal steroid use, singleton/multiple births, and birth weight, that may be utilized when counseling parents. (8,9) Gestational age, fetal weight, family values, and ongoing evaluation of fetal or neonatal conditions should guide resuscitation decisions. It is also guided by institutional policy and local/relevant law. The decision should not be based on gestational age alone.

During parental counseling on periviable birth, including the option that comfort care may be the most appropriate. Parents and professionals need to understand that choosing non-resuscitation is not a decision to provide no care but rather a decision to redirect care to comfort measures.

Electronic fetal heart rate monitoring should not be seen as an intervention but as a tool to guide decision-making. However, fetal monitoring is not synonymous with the need to perform a cesarean section or provide full resuscitation.

“According to the Cochrane Review for use of antenatal corticosteroids, published in 2020, corticosteroids are associated with a reduction in multiple severe neonatal outcomes, including perinatal death, neonatal death, and respiratory distress syndrome (RDS). Antenatal corticosteroids probably reduce the risk of intraventricular hemorrhage (IVH) and childhood developmental delay. (10) Based on this review, a single course of antenatal corticosteroids is recommended in women at risk for preterm birth.”

Antenatal Corticosteroids:

According to the Cochrane Review for use of antenatal corticosteroids, published in 2020, corticosteroids are associated with a reduction in multiple severe neonatal outcomes, including perinatal death, neonatal death, and respiratory distress syndrome (RDS). Antenatal corticosteroids probably reduce the risk of intraventricular hemorrhage (IVH) and childhood developmental delay. (10) Based on this review, a single course of antenatal corticosteroids is recommended in women at risk for preterm birth. Per their research findings, continued information is needed for the optimal timing of administration, which corticosteroid to use, and the potential benefits of subsequent courses.

Corticosteroids work by maturing many organ systems. (11) They increase the appearance of pulmonary surfactants and thereby decrease RDS. The corticosteroid effect on decreased IVH appears to be due to the enhanced circulatory stability in the vulnerable vascular germinal matrix and the subsequent protection from

alterations in cerebral blood flow. (12)

“According to the 2009 Cochrane review, antenatal magnesium is neuroprotective to preterm fetuses by decreasing the risk of cerebral palsy and gross motor dysfunction at two years of age. There was not a significant effect on childhood mortality or other childhood disabilities.”

Corticosteroids have the greatest efficacy within 2–7 days of anticipated delivery after the first dose. The current practice is administering corticosteroids in two doses, 24 hours apart. (13) The current dosing recommendation is betamethasone 12 mg q24h x 2 doses or dexamethasone 6 mg q12h x 4 doses. ACOG most recently updated their recommendation on antenatal steroid administration in 2021, stating that OB providers may consider administering corticosteroids between 22+0/7 to 22+6/7 weeks gestational age if resuscitation is planned after appropriate counseling. There may be a role for a shortened dosing interval if delivery is imminent and two doses, 24 hours apart, is not feasible. (14)

Per the ACOG 2017 committee opinion, OB providers may consider a single repeat (rescue) course of corticosteroids if the first course was more than 14 days and imminent delivery is suspected in the next week. (15) However, a recently published quality improvement project advocated for “rescue betamethasone” if the initial course was >7–10 days before expected delivery. (16)

“According to ACOG, to reduce maternal and neonatal infections and GA-dependent morbidity, a 7-day course of therapy of latency antibiotics is recommended during expectant management of women with preterm pre-labor rupture of membranes (PROM) for <34+0/7 weeks of gestation.”

Magnesium:

According to the 2009 Cochrane review, antenatal magnesium is neuroprotective to preterm fetuses by decreasing the risk of cerebral palsy and gross motor dysfunction at two years of age. There was not a significant effect on childhood mortality or other childhood disabilities. (17)

The mechanisms are not well understood, but several hypotheses have been made, including decreased excitotoxicity NMDA receptor antagonism, thereby decreasing excitatory neurotransmitters (such as glutamate). Additionally, magnesium may have anti-inflammatory effects, resulting in less oxidative stress and cytokine injury. (18)

ACOG supports the short-term (<48 hours) use of magnesium

sulfate for fetal neuroprotection in preterm delivery (<32 weeks) suspected to occur within 24 hours. In a trial looking at doses of magnesium, there was no difference in outcomes between 4 g versus 6 g; therefore, the recommended loading dose is 4 g. Continued magnesium maintenance may be given over the next 48 hours though current data do not specify the optimal duration of therapy before delivery. (19)

ACOG lists the absolute or relative contraindications for maternal magnesium as myasthenia gravis, severe renal failure, cardiac ischemia, heart block, and pulmonary edema. Alternative therapy may include levetiracetam, but efficacy is uncertain. (20)

Infection Screening:

According to ACOG, to reduce maternal and neonatal infections and GA-dependent morbidity, a 7-day course of therapy of latency antibiotics is recommended during expectant management of women with preterm pre-labor rupture of membranes (PROM) for <34+0/7 weeks of gestation. (21)

Preterm delivery complications following PROM may include clinical intra-amniotic infection, abnormal fetal testing, and significant abruptio placentae.

Best Practice Summary for Antenatal Care:

- Offer multidisciplinary counseling with OB/MFM, the NICU team, and parents when preterm delivery is a possibility.
- Use the NIH website for up-to-date survival and morbidity estimates.
- The parents may choose not to resuscitate between 22+0/7 to 23+6/7 weeks GA after counseling.
- Unless there is a significant or lethal known co-morbidity, recommend universal resuscitation beginning at 24 weeks GA.
- When resuscitation is planned: Antenatal steroids may be given starting at 22+0/7 weeks gestation
- Consider shorter interval steroids if delivery is imminent and two doses, 24 hours apart is not feasible.
- Consider a rescue course of steroids if the initial course was given >7–10 days from the expected delivery
- Magnesium (short term, <48 hours) beginning at 22+0 weeks GA for possible preterm delivery
- Routine fetal monitoring may begin at 22+0 weeks gestation
- Cesarean delivery would not be routinely offered before 23+0 weeks gestation, unless for maternal indications, after discussion as a multidisciplinary team with OB/MFM.
- A 7-day course of therapy of latency antibiotics is recommended during expectant management of women with preterm PROM <34+0/7 weeks of gestation.

DELIVERY ROOM MANAGEMENT:

When there is an impending delivery of an extremely premature infant, the NICU resuscitation team should lead the resuscitation. Specialized procedures and equipment checklists can be utilized for these deliveries to coordinate care and improve outcomes. A sample checklist is included in the Appendix. The NICU resuscitation team should brief the OB/MFM team on the resuscitation plan, including, but not limited to, the candidacy of delayed/deferred cord clamping and initial steps to be taken while the baby is still on placental support.

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Delayed/Deferred Cord Clamping:

Delayed/deferred cord clamping (DCC) is associated with many benefits for preterm infants, including reduced relative risk of death before discharge, improved transitional circulation, decreased need for blood transfusion, and decreased intraventricular hemorrhage. (22)

ACOG defines and recommends delayed cord clamping in both term and preterm for 30–60 seconds in vigorous infants. The AAP supports this statement and recommendation. The World Health Organization (WHO) recommends that the umbilical cord not be clamped earlier than 1 minute (60–180 seconds). The duration of DCC still needs further research, and some professionals may advocate for using signs of adaptation, such as ventilation, rather than an exact time. (23) Potential contraindications for DCC may include significant maternal bleeding, including separation of the placenta or compromised cord integrity.

The initial steps of newborn resuscitation should be started during DCC. Umbilical cord milking (UCM) continues to be researched, but a study published in 2015 was halted in 23–27 week GA premature infants due to increased risk of severe IVH. (24) There is not enough evidence to support or refute cord milking >32 weeks GA, and more research is needed on UCM <32 weeks GA safety. (25)

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Delivery Room Temperature:

Extremely premature infants lack brown adipose tissue and thereby cannot activate thermogenesis. Both hypothermia and hyperthermia can be harmful during the stabilization of extremely low birth weight (ELBW) infants. Every 1 °C below 36 °C on admission increases mortality by 28%. (26)

Hyperthermia also carries significant morbidity and mortality in ELBW infants, including changes in cerebral blood flow and the release of neuro-excitotoxic products. (27,28)

The World Health Organization (WHO) recommends setting

the delivery room temperature at 25 °C. (29) The Neonatal Resuscitation Program (NRP) guidelines recommend a delivery room (DR) temperature of 26 °C for infants < 1500 g. (30)

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Adjunctive Temperature Control Methods:

Heat loss in the delivery room includes convective, conductive, evaporative, and radiant heat loss. During the first few minutes of life, peak water loss occurs, resulting in a significant loss of heat and fluid. (31) Without drying, all ELBW infants should be placed in a polyethylene or polyurethane bag /wrap (e.g., NeoWrap) to prevent evaporative and conductive heat losses. (32) The infant should be placed immediately in the plastic wrap during delayed cord clamping.

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After the cord is cut, the infant should continue resuscitation under the radiant warmer while in the polyurethane bag, with an exothermic mattress placed underneath the infant. The head should be covered with a hat. Transfers of ELBW infants among beds and inter-hospital transfers provide additional risks of thermal stress. Resuscitation in an isolette is recommended to limit transfers from bed to bed.

Initial Oxygen during Resuscitation:

Use warm, humidified gases during resuscitation for infants <32 weeks of gestation. (30,33) For infants ≥35 weeks of gestation, start with an initial FiO_2 of 0.21. For infants 32–35 weeks of gestation, start with an initial FiO_2 of 0.21–0.3. For infants 32–35 weeks of gestation, there is not enough evidence to support a specific starting FiO_2 within the range of FiO_2 0.21–0.3. In two blinded RCTs comparing initial FiO_2 of 0.3 versus 0.6 or 0.65, there was a tendency toward an increased survival rate in the group with 0.3 initial oxygen. (34–36) For infants <32 weeks of gestation, start with an initial FiO_2 of 0.30. Target a SpO_2 of 80%–85% within 5 minutes, as failure to achieve this goal is associated with poor outcomes, including IVH. (37–39)

Intubation in the Delivery Room:

An attending physician, if possible, or a person most skilled at performing endotracheal intubation should be present for the resuscitation of ELBW infants. The most experienced resuscitation team member should intubate the ELBW infant.

“Intubation of ELBW should be reserved for those demonstrating persistent difficulty with transition after birth, after non-invasive measures such as PPV and oxygen. These indicators include but are not limited to, persistently low heart rate, high oxygen amount, and high pressures.”

The increased number of attempts at intubation increases the risk of IVH. (40) There should be no more than two attempts at intubation by any team member, if possible. An intubation attempt includes direct laryngoscopy and an attempt at passing the endotracheal tube through the cords. (40,41) Before any intubation attempt on ELBW babies, trainees, such as fellows, must demonstrate competency in independent procedures.

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Non-invasive Mechanical Ventilation (NIMV) During Resuscitation:

No convincing evidence shows that elective intubation confers any specific protective neurologic effects, and initial non-invasive ventilatory support should be considered the default. (42) Similarly, for infants <30 weeks, there is not strong data supporting any specific non-invasive method over another (CPAP vs. NIMV) with the currently available studies. The key is helping the extremely premature infant to acquire and maintain functional residual capacity (FRC). (43) However, given the equal lack of data showing harm, it may be pragmatic to utilize whichever mode that units feel more confident and comfortable with. (44–47)

Utilizing a CO₂ colorimetric detector with bag-mask-ventilation or T-piece ventilation during resuscitation may improve recognition of airway obstruction and may be an early indicator of improvement before changes in heart rate or saturation. (48,49)

“Therapeutic positioning and sound control start in the delivery room. Handling, touch, and noise may all represent noxious stimuli to an ELBW infant. An ELBW infant cannot self-regulate due to a lack of neurological organization during the third trimester. (50) Physiologic responses to these stimuli include changes in heart rate, respiratory rate, and saturation, which may be under-recognized.”

The Environment During Resuscitation:

Therapeutic positioning and sound control start in the delivery room. Handling, touch, and noise may all represent noxious stimuli to an ELBW infant. An ELBW infant cannot self-regulate due to a lack of neurological organization that would have occurred during the third trimester. (50) Physiologic responses to these stimuli include changes in heart rate, respiratory rate, and saturation, which may be under-recognized.

Several small studies are looking at the cerebral and systemic hemodynamic changes during periods of handling which suggest there may be early parenchymal abnormalities seen on ultrasound. (51)

Most studies have examined positioning, handling, and sensory integration during the NICU stay, but many do not report recommendations during the resuscitation period. It seems prudent to start protective interventions such as neutral (midline) positioning, decreased sound, gentle handling, minimal transferring, and early positional support (nesting) as soon as possible after delivery, beginning in the delivery room.

Best Practice Summary for Delivery Room Management:

- Set the resuscitation area to 25-27 °C.
- Deliveries should be attended by the NICU resuscitation team and include the attending physician if possible.
- The NICU and OB teams should discuss the resuscitation plan, including delayed cord clamping.
- Delayed cord clamping should be implemented for at least 60 seconds unless there is a clear contraindication.
 - Cord milking is not recommended in ELBW infants.
 - Resuscitation measures should be implemented during delayed cord clamping, including placing the infant in a plastic wrap/bag.
- Once the cord is cut, the resuscitation should continue using a radiant warmer while still in plastic wrap/bag.
 - Adjuncts to temperature control include thermal mattresses and hats.
- Place on servo warmer as soon as stable to avoid hypothermia and hyperthermia.
- Set starting FiO₂ at 0.21-0.30 (0.30 for infants <32 weeks GA),

and use warmed humidified oxygen for infants <32 weeks GA.

- Use a CO₂ colorimetric detector in line with mask ventilation when PPV is required.
 - Intubation, if required, should be done by the most experienced provider with no more than two intubation attempts per provider if more than one skilled provider is present.
- Therapeutic positioning, gentle handling, and sound control start in the delivery room.
- Ideally, the resuscitation bed should become the NICU care bed, if feasible, to limit bed transfers.

“There is currently insufficient evidence to support the optimal primary mode of non-invasive ventilation in extremely premature infants, and in particular, that choices impact the risk of mortality or bronchopulmonary dysplasia. (46,52,53) However, recent evidence suggests that NIMV may decrease the need for intubation, as well as decreased extubation failure, in the first week of life.”

RESPIRATORY MANAGEMENT

Non-invasive Ventilation:

Not all pre-term infants require intubation and mechanical ventilation at birth. There is currently insufficient evidence to support the optimal primary mode of non-invasive ventilation in extremely premature infants, and in particular, that choices impact the risk of mortality or bronchopulmonary dysplasia. (46,52,53) However, recent evidence suggests that NIMV may decrease the need for intubation, as well as decreased extubation failure, in the first week of life. (54–57)

For infants not requiring intubation, place infants on non-invasive mechanical ventilation using appropriately-sized nasal prongs or masks. (58) Occlusive binasal prongs and nasal masks have been shown to reduce the risk of CPAP failure and the incidence of nasal trauma. (59,60) The nasal mask and prongs may be alternated to prevent damage to the nose as long as functional residual capacity (FRC) is maintained during the switching of interfaces.

The continuation of NIMV or bubble CPAP is recommended until a minimum of 32 weeks CGA. (61) Consider continuing NIMV or bubble CPAP to extend to 34 weeks CGA to support FRC with possible benefits that persist to 40 weeks CGA. (61) Weaning off respiratory support is based on weight, stability of respiratory status, frequency of spells, and status of nares/septum.

Conventional Invasive Ventilation:

Volume-targeted ventilation (VTV) offers several advantages over pressure-limited ventilation (PLV). Therefore, assist-control volume guarantee is the preferred invasive conventional modality for respiratory support for the authors of this guideline.

A 2017 Cochrane Review showed that VTV modes resulted in a reduction of death or bronchopulmonary dysplasia (BPD) at 36 weeks CGA (RR: 0.73, CI 0.59–0.89), pneumothorax (RR: 0.52, CI 0.31–0.87), mean days of mechanical ventilation, rates of hypocarbia, Grade 3 and 4 IVH (RR: 0.53, CI 0.37–0.77), and combined periventricular leukomalacia (PVL) with or without grade 3 or 4 IVH (RR: 0.47, CI 0.27–0.8). (62) Normocarbia (45–55) should be maintained, hypocapnia avoided, and swings in PaCO₂ due to the vasoactive effect (dilation and constriction) of blood vessels in the brain.

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Tidal volumes should be initiated at 6 mL/kg and increased by 0.5 mL/kg to a maximum of 8 mL/kg unless the baby has a pneumothorax, pulmonary interstitial emphysema, or high settings on conventional mechanical ventilation before other ventilation modes should be considered. Initial ventilator frequency should be 30–40 bpm with PEEP at 6 cm. (63) The appropriate settings are not delineated for ELBW, particularly the most immature infants. In other populations, these settings have been discussed.

High-Frequency Ventilation:

Options for high-frequency ventilation (HFV) include High-Frequency Oscillatory Ventilation (HFOV), High-Frequency Jet Ventilation (HFJV), and High-Frequency Flow Interrupters (HFFI) (historically). Most comparative studies used the HFOV.

There is no clear evidence that early elective use of high-frequency ventilation offers any benefits over conventional ventilation and may cause harm. In a Cochrane Review, there was an inconsistent trend towards decreased chronic lung disease (CLD) in the HFOV group versus conventional ventilation. The same review showed an increased risk of pneumothorax and pulmonary interstitial emphysema (PIE) in the HFV group. There was no difference in IVH or PVL risks. All studies compared HFV to pressure-limited conventional ventilation. Both HFOV and HFFI were used. (64)

Direct comparison of HFV versus VTV has not yet been well studied. A systemic review comparing HFOV to HFJV failed to produce any relevant results. (65) Consider switching to high-frequency ventilation as a rescue mode for pneumothorax, pulmonary interstitial emphysema, and high settings on conventional mechanical ventilation (mean airway pressure >12 cm, increasing tidal volumes requirements persistently above >8 mL/kg).

Approach to Extubation:

Intubated infants should be assessed at least once daily for extubation readiness. This includes ventilator settings, gases, presence/absence of air leak around the endotracheal tube, and assessment of nares.

Early extubation (prior to 48 hours of life) in infants born 24–29 weeks gestation is not associated with an increase in severe

IVH compared to delayed extubation, even when considering re-intubation rates. (66) Studies are limited in infants 22–24 weeks GA. However, extubation failure is associated with an increased risk of death, prolonged respiratory support, and prolonged hospitalization. (67)

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Short-term dexamethasone may be considered if there is an absence or inadequate air leak around the endotracheal tube, particularly if the baby has been intubated for a prolonged period. (68) Other strategies may include short-term Lasix to improve pulmonary mechanics (69), fluid restrictions, and/or a caffeine bolus.

Early extubation (<48 hours) to CPAP is associated with decreased incidence of IVH and decreased incidence of re-intubation. (71) NIMV is associated with decreased extubation failure in the first week post-extubation compared to CPAP, but it does not affect chronic lung disease or mortality. (54,70)

“The Support Trial and Neoprom Meta-analysis showed increased mortality in the low saturation target group (85–89% vs 91–95%). The main driver of mortality seems to be necrotizing enterocolitis (NEC). CLD and retinopathy of prematurity (ROP) were higher in the high saturation target group. Reducing mortality is the clear priority, and target saturations should be 91-95%.”

Oxygen Saturation Targets:

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“The ELBW infants that require intubation should receive surfactant regardless of FiO_2 . Studies suggest improved outcomes with early (<2 hours of life) rescue therapy, including fewer pneumothoraces, severe IVH, and need for post-natal steroid therapy.”

Adjuncts to Respiratory Support:

Surfactant Administration:

The ELBW infants that require intubation should receive surfactant regardless of FiO_2 . (52,73) Studies suggest improved outcomes with early (<2 hours of life) rescue therapy, including fewer pneumothoraces, severe IVH, and need for post-natal steroid therapy. (74,75)

Surfactant should not be given until confirming appropriate endotracheal position by chest x-ray. Also, ensure careful movement and positioning while delivering surfactant, including keeping the head midline and avoiding rapid turning.

All intubated ELBW infants with a persistent oxygen requirement (such as FiO_2 greater than 0.3) and/or increased ventilator requirement (increasing PIP) may be considered for up to two additional doses of surfactant as early as 12 to 36 hours of life to minimize the risk of air leak, RDS, and morbidity and mortality. (76) In certain circumstances, one may repeat surfactant until the baby is 72 hours of life. Extended surfactant out to 2 weeks has no apparent benefit. Additional modalities of delivering surfactant, such as Less Invasive Surfactant Administration (LISA) or Minimally Invasive Surfactant Therapy (MIST), are being studied and may be available for delivering surfactant without intubation. These modalities may lead to improved outcomes, including BPD and IVH in ELBW. (77,78)

Caffeine and Control of Recurrent Apnea, Bradycardia, and Desaturation Episodes:

Caffeine is utilized as an adjunctive measure for the treatment of apnea of prematurity as well as BPD prophylaxis. Studies indicate that administering the first dose within 2 hours of life correlates with improved blood pressure and systemic blood flow. (79–83) The current caffeine dosing is a 20 mg/kg loading dose followed by 5–10 mg/kg with a maintenance dose every 24 hours for the course duration. (80)

Based on symptoms and overall physiologic maturity, the caffeine maintenance dose should be continued until the age of 34–36 weeks post-menstrual period. Some providers continue treatment beyond 36 weeks if apnea persists to prevent intermittent hypoxic events, improving neurologic outcomes. (84)

Recurrent apneas, bradycardia, and desaturations increase the risk of long-term adverse outcomes, including ROP and neurologic injury. When maximized non-invasive support fails (NIMV and caffeine), placing the infant back on the ventilator may be necessary. (85)

Vitamin A:

Supplementing very low birth weight infants with vitamin A is associated with a decreased risk of death or oxygen need at one month and oxygen requirement at 36 weeks post-conceptual age. There was no benefit in neurodevelopmental outcome at 18–22

months of age. (86) Small benefits should be weighed against the need for intramuscular dosing and repetitive, prolonged national shortages of available vitamin A preparations.

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Best Practice Summary Respiratory Management and Ventilator Strategies:

The initial modality for non-invasive mechanical ventilation is not yet elucidated, and units may choose CPAP versus NIMV based on comfort. Non-invasive mechanical ventilation should be continued until a minimum of 32 weeks CGA.

All ELBW infants who require intubation should receive surfactant as soon as a chest x-ray verifies the endotracheal tube position. These infants may be evaluated for additional doses of surfactant based on clinical status.

- Volume guarantee ventilation is the preferred mode of conventional primary ventilation.
- HFV can be considered rescue therapy or when air leak syndromes are present.
- Early extubation in eligible infants does not increase the risk of IVH.
- Caffeine should be started for apnea of prematurity and BPD prophylaxis.
- Routine O₂ saturation targets should be set at 91-95%.

EARLY NEONATAL CARE:

The following guidelines should be implemented at birth and continued for the first 72 hours to 1 week of life. Some experts advocate for dedicated small baby units. Such units include a dedicated zone with dark rooms, a quiet location, and a select group of providers trained and experienced in small baby care (i.e., NNP teams as front-line providers) and limiting resident trainee exposure. (16)

Fluids, Electrolytes, and Nutrition:

Prevent initial hypoglycemia by immediate initiation of IV glucose following delivery. It is essential to keep in mind the fact that glucose tolerance in the immature infant is decreased. Glucose delivery should be started at 4–5 mg/kg/min and titrated to tolerance. If glucose intolerance persists with glucose delivery at or slightly below 4, an insulin infusion may need to be considered. The safe upper tolerance for glucose delivery is ~12 mg/kg/min to

protect against liver disease.

“Some experts advocate for dedicated small baby units. Such units include a dedicated zone with dark rooms, a quiet location, and a select group of providers trained and experienced in small baby care (i.e., NNP teams as front-line providers) and limiting resident trainee exposure.”

Nutrition is critical for both somatic growth and brain development. The brain of the ELBW infant uses 50% of the required energy and quadruples its volume between 25 and 40 weeks. During this period, there is a remarkable increase in the proliferation, synaptogenesis, and connectivity of neurons and glial cells. (87)

Sufficient and well-balanced delivery of macronutrients is crucial. Glucose is the primary energy source for the brain, fat for membrane integrity and myelination; protein provides structural building blocks and signaling molecules, such as growth factors, neurotransmitters, and enzyme components, which are of utmost importance for brain growth and development. Adequate intake of essential micronutrients like iron, zinc, copper, iodine, phosphorus, and vitamins is also necessary for brain development and function.

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There are critical windows for mental development associated with nutrition intake. They describe specific fetal, neonatal, and infant life periods when deficient delivery of specific nutrients is associated with life-lasting effects on neurodevelopment. For example, it is well known that a deficiency in iodine or folic acid in the mother’s diet may lead to neurologic abnormalities in the fetus. It is also well described that low iron intake during the first year of life may lead to developmental delay. (88)

A crucial window is the preterm infant’s initial weeks, where rapidly developing systems and structures are at risk for under or aberrant development. Some of these systems are the cerebral cortex, basal ganglia, and hippocampus (important for learning and memory), myelin (responsible for the speed of processing), and cerebellum (important for balance, motor integration,

and cognition). (89) Neurodevelopment impairment inversely correlates with growth during NICU stay. (90–92)

Start of TPN during first hours of life. Parenteral solutions should initiate the delivery of protein (~3 gm/kg/day), glucose (~4–6mg/kg/min), and lipid emulsions (~2 gm/kg/day). Fish oil lipid emulsions (SMOF) contain DHA, which is important for premature infant lung, brain, and retinal development. Advance all macronutrient components to deliver 100–120 calories per kg daily within 1–2 weeks of life. Intake of total non-nitrogen to nitrogen calories should be balanced, achieving a ratio of 150–200 to promote lean body mass accretion. A direct correlation exists between linear growth and fat-free mass (not just weight) and higher Bayley mentation scores at school age. (93)

“Early start of TPN during first hours of life. Parenteral solutions should initiate the delivery of protein (~3 gm/kg/day), glucose (~4–6mg/kg/min), and lipid emulsions (~2 gm/kg/day). Fish oil lipid emulsions (SMOF) contain DHA, which is important for premature infant lung, brain, and retinal development. Advance all macronutrient components to deliver 100–120 calories per kg daily within 1–2 weeks of life. Intake of total non-nitrogen to nitrogen calories should be balanced, achieving a ratio of 150–200 to promote lean body mass accretion.”

The mother’s colostrum should be used to provide oral care. This has been proven to improve early immune responses and prepare the bowel to tolerate feedings by tightening enterocyte junctions. Mothers should be encouraged to express colostrum, starting at delivery, so infants can receive this treatment in the first few hours of life. In addition to providing colostrum for oral care, early hand expression and pumping after birth have also been shown to increase the mother’s milk supply to ensure adequate mother’s milk nutrition during the NICU stay and beyond. (97,98)

“Multiple immune modulators are found within human milk and are essential for establishing an infant’s initial healthy microbiome.”

Enteral feedings should be started early with mother’s milk with fortification. This strategy provides optimal nutrition and growth factors that lead to improved neurodevelopment. Every 10 ml per kg per day of mother’s milk increases Bayley II Mental Developmental Index (MDI) by ~0.6 points. (94) Mother’s own milk is preferred over donor milk as it is individualized for her baby and has not lost nutritional integrity to pasteurization or freezing. As soon as a volume of 50–100 ml/kg is tolerated, fortification of breast milk is mandatory to ensure the provision of extra calories,

protein, minerals, and vitamin intake. The presence of umbilical catheters or treatment with indomethacin is not a contraindication for enteral feeds.

Fluid intake should be adjusted to the clinical status need, considering the utmost need for nutrition delivery beginning day 1. As a general rule, crystalloid boluses should be avoided, optimizing environmental humidity to decrease insensible losses and the need for excessive additional fluids. (64,81) Parenteral fluids and enteral feed concentration improve the ability to deliver adequate nutrition despite fluid restriction.

High humidity is necessary to prevent insensible water losses and to regulate temperature and electrolytes. It is also of utmost importance to maintain skin integrity in these neonates. High humidity up to 85–90% is recommended for the first week of life at a minimum. (100) Weaning slowly down on humidity over the next few weeks to minimize fungal infection risk defines best practice. (101,102)

The disruption and interruption of ideal nutrition delivery must be minimized. TPN should be optimized each day, and prolonged periods of NPO should be avoided.

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Continue ongoing nutritional assessment for prompt identification and rapid correction of deficits.

Hematology:

Currently, studies are examining the neuroprotective effects of early erythropoietin and darbepoetin but have conflicting results. The last Cochrane Review published in 2021 does not recommend

routine early use of erythropoietin in preterm infants until further research elucidates outcomes. (103)

“A recent randomized trial for platelet transfusion showed that neonates in the high (>50,000) threshold group had an increased risk of death or major bleeding than the low threshold (>25,000) group. (112) Platelet transfusions in the extremely low birth weight neonate may be considered to maintain a platelet count > 25,000 or if there are signs of active bleeding until there are further studies.”

Coagulation protein synthesis begins in the fetus at 5–10 weeks gestation and is independent of maternal coagulation as these factors do not cross the placenta. (104) However, the development of the hemostatic system is age-dependent and matures with older gestational age. Studies are evaluating the immature coagulation system as a risk factor for IVH and possible therapeutic interventions. (105,106)

“Red blood cell transfusion thresholds comparing restrictive and liberal thresholds do not change morbidity and mortality, including death, bronchopulmonary dysplasia, retinopathy of prematurity and interventricular hemorrhage, or neurodevelopmental outcome at two years of age. (110,116,117) Restrictive transfusion guidelines differ in each study but range between 21–26 and up to 30% to maintain hematocrit.”

VLBW infants frequently receive at least one transfusion during their hospitalization. There are variable transfusion practices across the United States, and the optimal transfusion thresholds in neonates remain unclear. (107–110)

Thrombocytopenia is defined as $\leq 150,000$ and commonly seen in the NICU with an incidence of 18–35% at some point in the hospitalization. (109,111) Though thrombocytopenia is a risk factor for intraventricular hemorrhage during the first week of life, no correlation has been found between the severity of thrombocytopenia and the risk for IVH. A recent randomized trial for platelet transfusion showed that neonates in the high (>50,000) threshold group had an increased risk of death or major

bleeding than the low threshold (>25,000) group. (112) Platelet transfusions in the extremely low birth weight neonate may be considered to maintain a platelet count > 25,000 or if there are signs of active bleeding until there are further studies.

Fresh frozen plasma transfusions may be considered during signs of active bleeding or disseminated intravascular coagulation, but there does not seem to be a role in preventing intraventricular hemorrhage. (113–115)

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Per AAP Committee on Fetus and Newborn Policy Statement on Vitamin K, preterm infants with birth weight ≤ 1500 grams should receive 0.3 mg/kg to 0.5 mg/kg of Vitamin K intramuscular (IM) as prophylaxis. (118) Intravenous Vit K is not recommended.

Infection Screening

Though the rates of culture-proven early onset sepsis (EOS) in the United States have seemed to decline, the morbidity and mortality of these infections are high, particularly in extremely premature infants. (119) The clinical features of EOS are challenging to discern. Alternatively, the risk of prolonged antibiotic exposure carries a risk of poor outcomes. (120,121)

“ELBW neonates should be evaluated for EOS with consideration of starting antibiotics based on delivery risk factors such as preterm labor, prolonged rupture of membranes, and clinical chorioamnionitis. (120) Antibiotics, if started, can be discontinued if blood cultures are negative after 36–48 hours.”

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Multiple immune modulators are found within human milk and are essential for establishing an infant's initial healthy microbiome. (122,123)

Prophylactic systemic antifungals are effective against invasive fungal infection in extremely preterm infants. (124,125) Data on the safety, including the impact on fungal resistance and the long-term neurodevelopmental outcomes, is limited. (124,126) Additionally, newer studies are looking at the efficacy of oral nystatin prophylaxis as an alternative to systemic fluconazole. (127) Prophylactic fluconazole may be used in infants < 28 weeks gestation in a 4–6 week regimen to prevent systemic infection. (128)

Preventing Brain Injury:

Mechanisms of Brain Injury (129–131):

Cerebral pathology in extremely premature infants can present as white matter injury, such as periventricular leukomalacia (PVL) or periventricular-intraventricular hemorrhage (PIVH).

The following postnatal factors may be associated with brain injury: respiratory distress syndrome, hypocapnia due to inadvertent hyperventilation, hypotension, perturbations in arterial and venous pressure, and low cerebral blood flow (CBF). Hyperoxia, hypoxia, and fluctuations in cerebral oxygenation, indicative of poor cerebral autoregulation, can adversely affect brain development.

Premature infants with hypotension have CBF that is more affected by cardiac cycle changes than term infants. During diastole in a hypotensive preterm neonate, CBF is passive to diastolic blood pressure and is often absent. CBF autoregulation, when it occurs, is present during the systolic phase of the cardiac cycle compared to autoregulation of the mean and diastolic phases."

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The premature brain is vulnerable to oxidative stress from hypoxic-ischemic injury because of three risk factors: heart-rate-dependent cardiac output, the immature vascular supply, and disturbances in vascular autoregulation.

IVH Prophylaxis with Indocin:

In the Cochrane meta-analysis, prophylactic indomethacin

significantly reduced the incidence of severe intraventricular hemorrhage (typical RR 0.66, 95% CI 0.53 to 0.82). Meta-analyses found no evidence of an effect on mortality (typical RR 0.96, 95% CI 0.81 to 1.12) or a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months old (typical RR 1.02, 95% CI 0.90, 1.15). (132) Single-dose indomethacin prophylaxis (given within 12 hours after birth) is associated with decreased incidence of IVH, adjusted for gestation. (133,134)

Mirza et al., however, showed that indomethacin that was given ≤ 6 hours of life was not associated with decreased severity of IVH or death but was associated with decreased incidence of patent ductus arteriosus (PDA). (135) Prophylactic indomethacin therapy has become controversial due to a lack of a positive effect on long-term neurodevelopmental outcomes.

"There may still be a role in selective use for ELBW infants at higher risk of IVH, and a scoring tool (based on antenatal steroids, prematurity, sex, and other factors) based on individual hospital prevalence may guide the use of prophylactic indomethacin in high-risk infants. The Neonatal Quality Improvement Collaborative of Massachusetts has a scoring tool at: <https://www.neoqicma.org/sivh>."

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There is an increased risk of spontaneous intestinal perforation (SIP) with concomitant use of indomethacin and corticosteroids in very low birth weight infants (VLBW). (136) SIP in VLBW with co-exposure to steroids and indomethacin typically occurs in the distal ileum. (137) The timing of co-exposure with the highest risk for SIP is yet to be elucidated, but there is a significant increase if used together in the first postnatal week versus after the first week of life. (138,139)

IVH Screening:

Cranial ultrasound (HUS) has become the mainstay for screening symptomatic and asymptomatic injuries occurring in the neonatal period, particularly in ELBW infants. Early head ultrasound more often detects hemorrhages; later ultrasounds may detect white matter injury, particularly cystic periventricular leukomalacia (cPVL). (140) Ultrasound is highly sensitive to injuries surrounding the ventricles and blood products, which are echogenic but may not be the best modality for subtle white matter or parenchymal injuries. (141)

Most intraventricular hemorrhages occur early in the hospital course, with approximately 50% occurring in the first 8 hours of birth, and nearly all are apparent by the third day of life though they may occur in the first two weeks of life. (142) A screening HUS for all ELBW infants should be obtained by day of life 7 to detect silent

peri/intraventricular hemorrhages. An earlier head ultrasound may be obtained if an ELBW is symptomatic or has a profound clinical illness, such as an unexpected drop in hematocrit, hemodynamic instability, and increased and frequent apneic events.

Post-hemorrhagic hydrocephalus (PHH) is seen in 30-50% of infants with severe IVH and is typically detected on HUS 7–14 days after the bleed. (143) A repeat head ultrasound is recommended when an abnormality is detected. If there is a progressive disease, such as ventricular dilation, serial monitoring, such as weekly imaging, is indicated. Other head imaging modalities, such as magnetic resonance imaging (MRI) or computed tomography (CT), may be necessary later in the hospital course, such as closer to term gestation, pending the clinical team's discretion. However, MRI may be preferred.

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Best Practice Summary Early Neonatal Care:

- TPN should be started during the first hours of life. Parenteral solutions should deliver protein (~3 gm/kg/day), glucose (~6 mg/kg/min), and lipid emulsions (~2 gm/kg/day).
- Early start of enteral feedings with mother's milk with fortification is best practice. Donor human milk is preferred over formula when maternal breast milk is unavailable.
- Using a formal standard feeding schedule may decrease the risk for NEC.
- Fluid intake should be adjusted to the clinical status need, considering nutrition delivery needs.
- Overall growth should be monitored and optimized, including linear growth, head circumference, and possibly body composition, early in the hospital course to improve neurodevelopmental outcomes.
- All preterm infants should receive Vitamin K prophylaxis at 0.3 mg/kg to 0.5 mg/kg IM to a maximum of 1 mg IM (term dose). Intravenous Vit K is not recommended.
- Fluconazole prophylaxis is recommended for candida

prophylaxis in infants < 28 weeks.

- In units that consider indomethacin for IVH prophylaxis, a risk-based strategy may be appropriate to minimize harm and direct therapy to the highest-risk neonates.
- If prophylactic indomethacin is administered, caution should be used if administered with concomitant corticosteroids, and a high suspicion for possible SIP should be maintained.
- A screening HUS should be obtained on day seven or sooner if clinical instability and high suspicion of a bleed are noted.
- If there is a concern for PHH, serial HUS should be obtained.
- If there is a high concern for PVL, an MRI is more sensitive than a HUS.
- Monitor and optimize overall growth, including linear growth, head circumference, and possibly body composition, early in the hospital course to improve neurodevelopmental outcomes.

HEMODYNAMICS:

Hemodynamic instability is common in preterm infants and is associated with an increased risk of IVH. The traditional parameters, such as heart rate (HR), blood pressure (BP), capillary refill time (CRT), serum lactate, and urine output, to evaluate hemodynamic instability lack sensitivity and specificity.

These are proxy parameters of cardiovascular well-being. Furthermore, there is a lack of consensus on the actual definition of hypotension or the appropriate BP range in preterm infants.

"Cerebral blood flow is affected by systemic vascular resistance and pulmonary vascular resistance, cardiac output, end-organ resistance of the brain, and the effects of therapy on circulation. There is no consistent link between BP and poor neurodevelopmental outcomes. Concurrent continuous blood pressure and near-infrared spectroscopy (NIRS) monitoring can be used to detect loss of cerebral autoregulation."

Cerebral Autoregulation:

Cerebral autoregulation is a physiologic mechanism that holds cerebral blood flow relatively constant across changes in cerebral perfusion pressure. Cerebral blood flow (CBF) autoregulation is functional in normotensive infants; however, this may not be the case in a hypotensive VLBW infant, in whom CBF may become pressure passive. (129) Dysregulation of cerebral blood flow significantly contributes to the risk of IVH and white matter injury, making it essential to optimize brain perfusion. (129) BP is a poor surrogate for cerebral blood flow. (62)

Cerebral blood flow is affected by systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), cardiac output (CO), end-organ resistance of the brain, and the effects of therapy on circulation. There is no consistent link between BP and poor neurodevelopmental outcomes. Concurrent continuous blood pressure and near-infrared spectroscopy (NIRS) monitoring can be used to detect loss of cerebral autoregulation. This loss of autoregulation should prompt the evaluation of etiologies leading to such a compromise.

Cerebral NIRS may better reflect adequate cerebral oxygen delivery than arterial oxygen saturation (SpO₂) alone during the immediate transition period. Cerebral NIRS measures will be affected by inadequate systemic oxygenation and hemodynamic instability, anemia, and hypocarbia. Addressing these factors may have implications for improving cerebral oxygenation. (144)

Limited data have demonstrated an association between early cerebral oxygenation measures and the development of IVH and longer-term neurodevelopmental outcomes. (145) Early continuous cerebral NIRS monitoring in very preterm infants revealed an association between lower cerebral oxygen saturation and the primary adverse outcome of death before hospital discharge or severe neuro-radiographic brain injury. (145) Alderliesten found that regional oxygen saturation (rSO₂) <55% was significantly associated with severe IVH and that 20% of time spent with rSO₂ of <55% in the first postnatal 72 hours was also associated with death or unfavorable cognitive outcome at 24 months. (146)

Blood Pressure Monitoring:

Hypotension is blood pressure (BP) below the 5th or 10th percentile for gestational and postnatal age. Historically, in weeks, blood pressure has been targeted at or above gestational age. Correlation to CBF is now supported. This definition should only be considered in conjunction with other markers of tissue perfusion before initiating therapies.

Figure 1 shows the systolic blood pressure range seen in babies of 24 to 40 weeks of gestation when (A) 4 to 24 hours old and (B) 10 days old. (147)

The above blood pressure values can be used as objective values

to help identify babies needing further assessment to determine circulatory compromise and guide therapy. Continuous blood pressure monitoring via arterial catheter should be done at least during the initial transitional period of 72 hours after birth in the critically ill neonate.

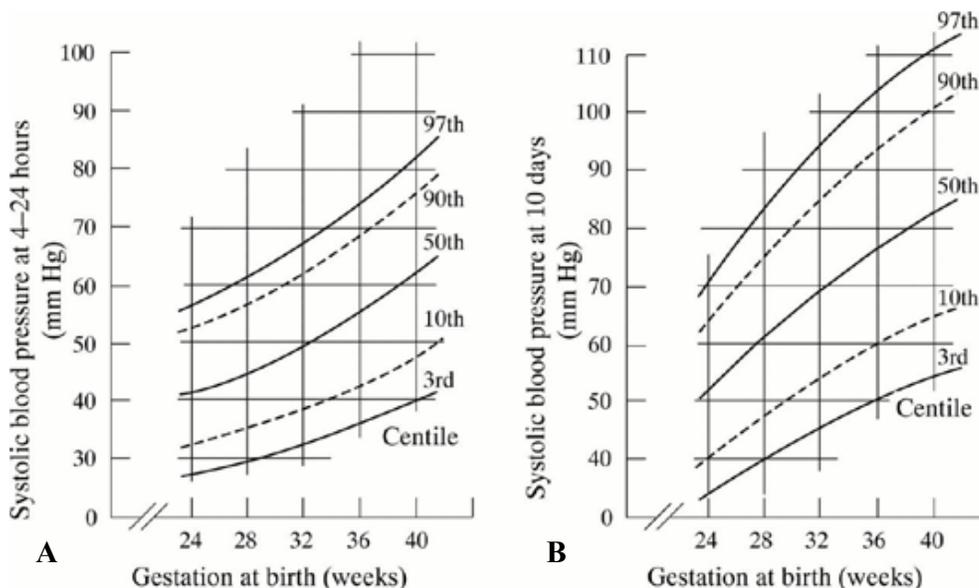
“Care must be taken to avoid sudden changes in cerebral blood flow. Attempts must be made to avoid frequent and rapid flushes or fluid boluses. Care should be taken in titrating pressor medication drips to avoid wide swings in blood pressure. Ventilator management should include strategies to avoid wide swings in PaCO₂.”

Noninvasive arterial blood pressure assessment using oscillometry frequently overestimates arterial BP and should be used cautiously. This method may be sufficient for assessment in a stable neonate. In addition to the mean BP, attention should be paid to the systolic and diastolic pressures to direct management.

Care must be taken to avoid sudden changes in cerebral blood flow. Attempts must be made to avoid frequent and rapid flushes or fluid boluses. Care should be taken in titrating pressor medication drips to avoid wide swings in blood pressure. Ventilator management should include strategies to avoid wide swings in PaCO₂.

Infants at increased risk of IVH and hemodynamic instability should have a comprehensive hemodynamic evaluation that should include meticulous examination, review of traditional parameters (as above), functional echocardiography (to assess preload, afterload, and cardiac contractility, estimation of cardiac output), and assessment of end-organ perfusion using NIRS.

Figure 1: Systolic BP ranges in 24–40 wks GA



Comprehensive multi-modal hemodynamic monitoring will allow for understanding the physiology better and help understand which infants develop IVH. There is a need for further research to evaluate “optimal cerebral perfusion pressure,” and adopting multi-modal monitoring tools (including traditional parameters + functional echo + NIRS) is the way forward.

Near Infrared Spectroscopy (NIRS):

Near-infrared spectroscopy (NIRS) measures the combined effects of tissue oxygenation, perfusion, and oxygen extraction. It can provide information on end-organ perfusion and oxygenation by providing a direct, continuous, and absolute estimate of the tissue oxygen saturation (rSO₂). Cerebral blood flow (CBF) autoregulation is functional in normotensive infants. However, this may not be the case in a hypotensive VLBW infant, in whom CBF may become pressure passive. Concurrent continuous blood pressure and NIRS monitoring can be used to detect loss of cerebral autoregulation. This concern should prompt the evaluation of etiologies leading to such a compromise.

“When feasible, all VLBW infants should receive continuous multi-organ (cerebral and renal) rSO₂ monitoring using NIRS in the first 72 hours of life and subsequently, if a hemodynamic compromise is suspected. Normal rSO₂ range is dependent on the sensor type used at the institution.”

When feasible, all VLBW infants should receive continuous multi-organ (cerebral and renal) rSO₂ monitoring using NIRS in the first 72 hours of life and subsequently, if a hemodynamic compromise

Table 1 Abnormal CrSO₂: Potential Causes and Clinical Interventions (from Plomgaard) (152)

Change in Cerebral Oximetry (rSO ₂)	Potential Causes	Clinical Interventions
CrSO ₂ <60% (risk of hypoxemia)	Cardiac, CNS, or vascular anomaly	Correlate with other clinical findings. Consider congenital heart disease. Evaluate for seizures?
>20% decrease below baseline	Decreased O ₂ delivery to the brain	<u>Anemia</u> – transfuse pRBCs Low arterial oxygen saturation – increases FiO ₂ <u>Hypotension</u> – raises BP, improves cardiac output Hemodynamically significant PDA – close. Low pCO ₂ (increase pCO ₂) – correct hypocarbia, avoid high vent mean airway pressure Possible pneumothorax? Infant’s head positioning (impeded cerebral venous outflow)?
	Increased O ₂ consumption	CNS issue – treat pain and agitation; sedate appropriately. Evaluate for seizures Febrile? – treat fever, hyperthermia
CrSO ₂ > 85% >20% Increase above baseline	Increased O ₂ delivery	Hyperoxia/hypercapnia – correlate with pulse oximetry and decreasing FiO ₂ as needed
	Decreased O ₂ extraction	Over-sedation – evaluate for excess sedation. Severe CNS injury – evaluate for cortical tissue death or perinatal asphyxia Pulmonary hypertension Apnea Cares
	Hypoglycemia	Treat low blood glucose.
	SGA	

is suspected. Normal rSO_2 range is dependent on the sensor type used at the institution. In literature, normal values are typically between 55% and 85% (the normal range is sensor-dependent). Renal rSO_2 readings are typically 5–15 points greater than cerebral rSO_2 readings. (148–150)

There is an inverse relationship between cerebral rSO_2 ($CrSO_2$) and gestational age, and it also decreases with postnatal age. (151) Each infant's $CrSO_2$ reading should be compared to the baseline and range; variation within this reference range may indicate dysregulation of brain oxygenation. Consider a response to changes in rSO_2 values 20% above or 20% below the infant's baseline (see Table 1). (152)

Echocardiogram:

An early comprehensive echocardiogram within 72 hours after birth can help establish structural normality and evaluate the transitional circulation. This screening will help with further focused assessment using functional echocardiography in infants with hemodynamic instability. A hemodynamically significant PDA has been associated with IVH, acute pulmonary hemorrhage, NEC, and BPD. (153) Subsequent functional echocardiography (POCUS: point of care ultrasound) can help in the hemodynamic evaluation of infants with PDA, shock, or other causes of hemodynamic instability. (154,155) Functional echocardiography can offer additional information on organ blood flow.

“A hemodynamically significant PDA has been associated with IVH, acute pulmonary hemorrhage, NEC, and BPD.”

Functional echocardiography can also provide information on global myocardial function, intravascular volume status, pulmonary hypertension, and PDA. The presence of PDA should encourage further prompt evaluation for signs of left atrial overload and compromise of the systemic circulation. Measures such as left ventricular output (LVO) and right ventricular output (RVO) can be unreliable in a newborn in the presence of shunts (PDA and PFO).

“Serial assessments with functional echocardiography and continuous rSO_2 measurements using NIRS should be used to direct the management of PDA.”

Serial assessments with functional echocardiography and continuous rSO_2 measurements using NIRS should be used to direct the management of PDA.

Management of Hemodynamic Compromise:

Hemodynamic instability should be managed based on altered physiology and a precise individualized approach. The traditional pressure-driven approach relies on surrogate markers of cardiac output, which are neither reliable nor evidence-based.

Functional echocardiography may help adopt a physiology-based approach to treatment in infants with hypotension or shock. This modality may assist in choosing fluid resuscitation therapy versus inotropic support. When inotropic support is chosen, functional echocardiography may inform the provider of the appropriate

choice of inotrope or vasopressor therapy based on preload, afterload, and cardiac function assessment. Ideally, it should be used to evaluate all infants with shock or needing two or more inotropes.

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Pharmacological Treatment of Neonatal Shock (see Table 2):

Inotropes/vasopressors are ideally given via a central venous line. Blood pressure fluctuations are associated with the development of cerebral lesions and should be avoided.

A time delay should be considered (approximately 20 minutes) after the initial administration, and do not rush increasing the dose if there is no effect within this timeframe. Inotropes/vasopressors must be titrated according to the response on mean ABP (i.e., mean ABP reassessed in 15-20 minutes after dose adjustment).

Reperfusion injury plays a role in intraventricular hemorrhage. Consequently, hypertension should be strictly avoided.

An echocardiogram should be obtained in refractory cases to evaluate cardiac structure and function.

Hydrocortisone may be helpful in preterm babies and refractory cases of hypotension.

Other causes in refractory cases should be considered: high MAP, pneumothorax, effects of drugs like opioids/paralytic agents, and others that may cause physiologic impairment of CO.

Best Practice Summary Hemodynamics:

- Infants at increased risk of IVH and hemodynamic instability should have a comprehensive hemodynamic evaluation that should include meticulous examination, review of traditional parameters (such as heart rate [HR], blood pressure [BP], capillary refill time [CRT], serum lactate, urine output and arterial oxygen saturation [SpO_2]), functional echocardiography (to assess preload, afterload, and cardiac contractility, estimation of cardiac output) and assessment of end-organ perfusion using NIRS.
- The physiology-based approach is best to target specific etiopathology leading to hemodynamic compromise.

Neuroprotective Family Centered Developmental Care:

Time in the NICU environment is associated with many stressors placed on fragile and developing premature neonates, including care times, procedures, harsh and loud sounds, and lighting, all of which have negatively impacted neurocognitive and behavioral outcomes. (156) Neuroprotective family-centered developmental care for extremely premature infants has been shown to improve the outcomes of these infants. (157,158) The final stages of fetal brain development, including organization, synaptogenesis, and myelination, begin during the third trimester. During this time, sensory networks are establishing appropriate connections. (159) An integral aspect of care is providing a healing environment to support the formation of these neural networks while in the artificial extra-uterine environment of the NICU.

"A time delay should be considered (approximately 20 minutes) after the initial administration, and do not rush increasing the dose if there is no effect within this timeframe. Inotropes/vasopressors must be titrated according to the response on mean ABP (i.e., mean ABP reassessed in 15-20 minutes after dose adjustment)."

Neuroprotective Care During and Immediately After Delivery:

The use of slow and gentle movements helps to protect the vestibular system and minimize stress. Keeping the baby's head midline and limbs flexed, supported by soft boundaries to mimic the fetal position, also helps minimize stress, decrease energy

expenditure, and support physiologic stability. (134)

One study found a significant decrease in tissue hemoglobin and oxygen index during head rotation in infants <26 weeks gestation. (160) A second study found a significant cerebral blood volume (CBV) increase during 90-degree head rotation, pronounced in infants <1200 g. (161) A third study found cerebral blood flow velocities were significantly higher in the supine or prone position. (162)

Keeping the baby in a horizontal position with feet at the level of the head during movement and diaper placement helps to prevent sudden increases in intracranial pressure and blood flow. Diaper changes can be done in a side-lying position to accomplish this goal. A hat can keep the baby's eyes covered and protect them from direct light during resuscitation and care. Ambient light should be kept to a minimum needed for care and procedures. Monitoring noise levels and keeping voice levels low helps to maintain a calm environment and prevent stress from loud sounds.

Neuroprotective Care Throughout the NICU Stay:

Preterm infants' eyes should always be protected from bright light until 32 weeks postmenstrual age (PMA) due to the absence of pupillary reflex. After 32 weeks of PMA, incubator covers can be removed during the day to allow for diurnal variation. (163) All infants' eyes should be protected from direct bright lights during exams and procedures.

Preterm and sick infants should be protected from loud sounds. (164,165) The AAP recommends that sound levels remain below the maximum level of 45 decibels. (166) Excessive noise levels may impair the appropriate development of the auditory cortex and interfere with language development. (167) Loud sounds interrupt sleep and increase stress, interfering with healing and growth. Parents should be encouraged to talk and/or sing softly but directly to their baby during short awake times, which has been shown to promote language development at 18 months CGA. (168) Alarm volumes should be turned to minimum, easily heard levels, and turned off quickly to reduce sound levels further.

Table 2. Pharmacological treatment of shock based on etiology

<u>Etiology</u>	<u>Underlying pathophysiology</u>	<u>First line treatment</u>	<u>Second line treatment</u>
Sepsis/NEC	↓SVR, ↑CO, capillary leak, and relative intravascular hypovolemia	Volume (crystalloid, blood products) Norepinephrine	Vasopressor agents: Dopamine (max 10 mcg/kg/min) Vasopressin
PDA	↑ Pulmonary flow ↓ Systemic flow	Consider ductal closure Limitation of left-to-right shunt by strategies to increase PVR (e.g., permissive hypercapnia, ↑PEEP).	Dopamine (if PDA is being treated after 72 hours) Dobutamine may be 1 st line if there is RV/LV dysfunction
Hypovolemia (less common- check for h/o blood loss/IVH)	Low filling, ↓CO	Volume (crystalloid, blood products)	
Post PDA ligation	LV systolic dysfunction and high afterload	Milrinone	Dobutamine
Hypoxic- ischemic injury	LV and/or RV systolic dysfunction, PPHN	Dobutamine	Low dose Epinephrine

Protecting the preterm infant's muscles from extensor contractures can be done by supporting a flexed position with soft boundaries to maintain the "fetal position" of the womb. Softly containing limbs helps to prevent excessive energy loss by minimizing uncontrolled flailing of the infant's limbs. Softly molded positioning aids placed under the infant's head can help avoid/minimize abnormal head molding. Headgear used to secure non-invasive nasal ventilation must be closely monitored to avoid abnormal head molding.

"Keeping the baby's head midline and limbs flexed, supported by soft boundaries to mimic the fetal position, also helps minimize stress, decrease energy expenditure, and support physiologic stability."

Efforts should be made to minimize painful procedures and to provide adequate nonpharmacological and pharmacological analgesia as needed. Clustering cares, exams, and procedures should be done whenever possible to protect sleep, which is essential for healing and growth.

Exams, nursing cares, and especially painful procedures for infants <32 weeks CGA or critically ill should be done with two-person/four-handed handling to maintain physiologic stability. Parents can be encouraged to be one of the persons to help provide support whenever possible. Parent-infant bonding and attachment should be supported at every opportunity, which is essential for optimal brain and emotional development. (169,170) Parents should be encouraged to be actively involved in their baby's daily care and understand their infant's unique behavioral cues to facilitate bonding and attachment.

"Keeping the baby in a horizontal position with feet at the level of the head...helps to prevent sudden increases in intracranial pressure and blood flow...Ambient light should be kept to a minimum needed for care and procedures. Monitoring noise levels and keeping voice levels low helps to maintain a calm environment and prevent stress from loud sounds."

Skin-to-Skin Contact:

Skin-to-skin contact (SSC), sometimes called Kangaroo Care, has improved outcomes, including clinical stability (temperature, glucose, respiratory and hemodynamic) through enhanced vagal tone. (171-173) The impact of improved vagal tone, in turn, has many long-term outcomes, including improved prosocial behavior, emotional regulation, improved health, and developmental outcomes. (156,174)

Early SSC also improves breastfeeding establishment and duration,

benefits maternal bonding, improves mental health, and reduces stress. (175) SSC in the first 72 hours of life has not been shown to increase the incidence of severe IVH. (175,176) Intubation is NOT a contraindication for skin-to-skin care but requires more staff support to transfer the infant from the bed to the parent's chest. If an infant is intubated, a reclining chair or rocking chair, with rockers wedged to prevent rocking, should guard against inadvertent extubation (otherwise, parents will instinctively rock).

"Preterm and sick infants should be protected from loud sounds. The AAP recommends that sound levels remain below the maximum level of 45 decibels. Excessive noise levels may impair the appropriate development of the auditory cortex and interfere with language development. Loud sounds interrupt sleep and increase stress, interfering with healing and growth. Parents should be encouraged to talk and/or sing softly but directly to their baby during short awake times, which has been shown to promote language development at 18 months CGA.."

Best Practice Summary for Neuroprotective Family-Centered Developmental Care:

- Neuroprotective care for the extremely premature infant includes a family-centered approach which begins in the delivery room and is extended throughout the entire hospital stay.
- A healing environment should protect the preterm infant's development sensory system, including protection from loud noise, bright lights, and pungent odors.
- Positioning should support flexed, midline "fetal" posture with soft boundaries to decrease stress, support sleep, and prevent extension contractures.
- Stress and pain should be minimized to support hemodynamic stability and minimize sudden cerebral blood flow fluctuations.
- Mothers should be supported in providing expressed breast milk for optimal brain development and immune protection.
- Optimal physiologic stability and parent-infant bonding/attachment should be augmented with early, frequent, and prolonged skin-to-skin contact.
- Parents should be encouraged to softly talk (or sing) to their preterm babies during awake times to support emotional connections and language development.

Appendix 1: Small Baby Supplemental Resuscitation Checklist

Small Baby Supplemental Resuscitation Checklist (<30 weeks GA and/or <1,000 grams)

<u>RT Equipment</u>	<u>RN/MD Equipment</u>	<u>Resuscitation Plans</u>
<ul style="list-style-type: none">• 42 mm Extra Small mask <u>attached</u> to Neo-puff• FiO₂ set to 30%• Suction catheter <u>attached</u> to suction tubing• 00 Laryngoscope blade with 2.5 and 3.0 ETT• Ensure Curosurf available• NIMV prepared with Fisher-Paykel interface	<ul style="list-style-type: none">• 2nd RN present (check room temp and dim lights)• Isolette used (pre-warmed to 36.8° and H₂O tank filled)• Sterile Neowrap given to OB scrub nurse• Bunting, chuck, and hat bundle prepared• Suction decreased to 60 mmHg• Order Fluids/Meds: TPN/lipids, 0.45 NaAcetate, Caffeine (Goal all given by 2hrs)	<ul style="list-style-type: none">• OB and NICU provider to perform delayed cord clamping• Support/contain, stimulate, welcome infant during DCC• Blot chest, place ECG leads first, then place pulse ox• Wrap infant completely and keep midline position• Start CPAP 5 immediately• Place hat, cover eyes, take temp and place temp probe

“Skin-to-skin contact...has improved outcomes, including clinical stability (temperature, glucose, respiratory and hemodynamic) through enhanced vagal tone. The impact of improved vagal tone, in turn, has many long-term outcomes, including improved prosocial behavior, emotional regulation, improved health, and developmental outcomes.”

Appendix 2: Tiny Baby Delivery and Golden Hour Checklist

Mins		Time Completed	Reason for Variance	Q.I.
0	Place baby in preheated Neohelp wrap (for transitional nursery, give OR nurse unopened sterile Neohelp wrap to use during delayed cord clamping), keep midline with head/body level on mother on Life Start table. Have OB perform 60 seconds of delayed cord clamping or cord milking per protocol			Delayed cord clamping Y/N Secs
1	Provide gentle stimulation and welcome baby in a soft voice Place Neo-wrapped baby in bunting, keeping midline and level, limbs flexed, moving slowly and talking softly Start resuscitation per NRP guidelines Start Neopuff CPAP 5 or PPV 18-22/5 depending on RR, HR, and chest rise (Attempt to avoid intubation for a minimum of 3 mins of life with effective ventilation/CPAP delivery. Consider increasing pressure and i-time before intubation) Place ECG leads on the chest first, then place a pulse ox on the right wrist.			Cord milking Y/N
2	Place warmed hat (cover eyes to protect from light), then adjust room lights to normal.			
3	Take vitals, including temperature, place temp probe, and switch isolette to the correct baby mode.			Initial Temp °C
5	Place gavage tube once HR and saturations are stable			
5-10	Obtain cord blood labs (type and screen, blood culture, CBC w/ diff, procalcitonin) Set up and apply respiratory support device (BCPAP, NIMV, VG/AC) Finish preparation and start placement of umbilical lines Assess respiratory status and administer surfactant as needed (all intubated infants should receive surfactant after chest x-ray)			Labs drawn from cord Y/N CPAP _____ NIPPV _____ Vent _____ Surfactant Y/N
10-15	Obtain measurements (Wt, Length, HC) if the infant is stable Prime Starter TPN and A-line fluids Notify the unit secretary and TL1 of the admission			
15-50	Place PIV Begin infusion of starter TPN and A-line fluids Give caffeine loading dose within 2 hours of birth (<32 wks) Once umbilical lines are placed, obtain remaining labs, blood glucose, and blood gas Call secretary to page for x-ray tech, obtain chest and abdominal 2V X-ray (chest x-ray must be done prior to surfactant administration) Give vitamin K and erythromycin as ordered Give antibiotics if indicated			UVC successful Y/N UAC successful Y/N UVC completed: _____ UAC completed: _____ 1st Glucose: ____ Time: _____ TPN started: _____ Caffeine given: ____ Abx given: _____

Appendix 2 (cont'd)

50-60	<p>Close the isolette and check that humidity is turned on starting at 85%</p> <p>Transfer to the tiny baby unit in the same isolette as used for resuscitation</p> <p>Send admission labs</p>			
Post Golden Hour	<p>Obtain temperature</p> <p>Elevate HOB</p> <p>Remove Neohelp wrap once 85% humidity is reached and the baby's temperature is stable.</p> <p>Debrief with all delivery team members</p> <p>Update parents and encourage early SSC</p> <p>If not contraindicated, encourage the mother to pump colostrum and emphasize the importance of human milk for preterm infants.</p> <p>Start oral care with colostrum as soon as available.</p>			<p>The time arrived in NICU:</p> <p>Admission Temp: °C</p>

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