EPIQ CONSENSUS GUIDELINES ON EARLY NEUROPROTECTION BUNDLE – UPDATED 2026

Purpose: This document is intended to provide evidence-informed best practice guidelines for neuroprotection and the prevention of intraventricular hemorrhage (IVH) in preterm infants **less than or equal to 29 weeks** of gestational age at birth **in the first 7 days of life**.

Goal: The goal is to promote consistent neuroprotective care that improves outcomes for vulnerable preterm populations through multidisciplinary engagement and system-level change.

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Key Definitions: Clinical practices associated with a reduction in the risk of IVH have been classified as:

- **Interventions**: Any pharmacological or non-pharmacological intervention that directly prevents IVH by stabilizing immature physiology.
- **Enablers**: Any strategy that indirectly reduces the incidence of IVH by mitigating the risk of causal pathways.

Strength of Recommendations	Interpretation	Clinical Application
Strong recommendations	The desirable effects (lower brain injury) of an intervention clearly outweigh the undesirable effects	applicable to most individuals and should be followed as the standard of care
Weak/conditional recommendations	Desirable (lower brain injury) and undesirable effects are closely balanced OR Available evidence is of low certainty	recognize that different options may be appropriate for different individuals or situations Shared decision-making, considering individual values and preferences, is essential

Adapted from: Prasad, M., & Schünemann, H. J. (2024). Introduction to the GRADE tool for rating certainty in evidence and recommendations. Clinical Epidemiology and Global Health, 29, 101234

What is covered in this document:

- The focus of this document is to support the implementation or adoption of best practices aimed at the neuroprotection and neuropromotion in preterm infants ≤ 29 weeks' gestational age at birth
- The best practices are focused on the early perinatal period and the first 7 days of life
- Like most previous care bundles, not all interventions or enablers will necessarily have the same level of evidence supporting them. The purpose of this document is to highlight best-practice elements from each domain and provide a brief overview of the evidence base.

Table 1: Key Clinical Domains of Best Practices are listed below

Antenatal Care	Clinical practices in the antenatal period and around the time of preterm birth
Delivery Room Care	Clinical practices in the delivery room and around the first 1-2 hours of infant stabilization
Systemic Management	Clinical practices around respiratory, hemodynamic, fluid balance, and metabolic management in the NICU during the first 7 days of life
Care Environment	Clinical practices around developmental positioning, handling, ambient noise and lighting in the NICU space during the first 7 days of life
Invasive procedures	Clinical practices encompass bloodwork stewardship, infusion and bolus administration, and pain and stress management during procedures.
Parental Engagement	Clinical practices that encourage parental involvement in care and strengthen parent-infant bonding

Table 2: Summary of Interventions with strength of recommendations

Interventions: Any pharmacological or non-pharmacological intervention that directly prevents IVH by stabilizing immature physiology.

Clinical Domain	Intervention	Strength of Recommendation
Antenatal Care	Offer Antenatal Steroids to women at risk of preterm birth within 7 days at or beyond 22 weeks of gestation, where active resuscitation is planned. *	**Strong recommendation** (moderate certainty of evidence)
	Maximum survival benefit of Antenatal Steroids peaks at 12 hours and continues till 14days of birth, but no differential impact of timing of steroids on the risk of IVH. **	Weak recommendation (low to very low certainty of evidence)
	Administer intrapartum prophylaxis for threatened preterm labour with unknown Group B streptococcus status or positive Group B streptococcus swab, ideally > 4 hours before birth. ***	Weak recommendation (low certainty of evidence)
	Offer magnesium sulphate for fetal neuroprotection to women at risk of imminent preterm birth. At the threshold of viability, use should be individualized and linked to a plan for active neonatal resuscitation. *	**Strong recommendation** (high certainty of evidence for neuroprotection overall; low-to-moderate certainty for the exact lower gestational-age threshold at the limits of viability)
Delivery Room Care	Allow deferred cord clamping for 60 seconds in vigorous preterm infants when feasible. Cord milking in infants <28 weeks' gestation is not recommended.	**Strong recommendation** (high certainty of evidence to improve survival, low certainty of evidence that it has effect on IVH, low certainty of evidence

		that cord milking increases risk of severe IVH)
	Non-invasive respiratory support (e.g., CPAP) is recommended as the primary mode of respiratory support for spontaneously breathing preterm infants born at ≥24 weeks' gestation.	**Strong recommendation** (moderate certainty of evidence for respiratory morbidity, but low certainty of evidence for incidence of IVH)
Systemic Management	If using a conventional form of mechanical ventilation, volume-targeted ventilation (VTV) as an adjunct is recommended in the first 72 hours of life	**Strong recommendation** (moderate certainty of evidence)
	Intramuscular Vitamin K (0.5 mg) is recommended.	**Strong recommendation** (based on consensus and current Canadian Pediatric Society Recommendations but low to very low certainty of evidence). Insufficient evidence to support intravascular Vitamin K.
Parental Touch	Encourage EARLY skin-to-skin care using a two-person transfer process. If skin-to-skin care is not feasible, encourage positive parental touch such as hand hugging/containment. Involve parents in facilitated tucking and calming during routine care and painful procedures. The need for minimal handling or midline positioning should not, by itself, preclude skin-to-skin care. ****	**Strong recommendation** (moderate to high certainty of evidence)

*If parents wish to resuscitate the infant at 22 weeks, consider giving antenatal steroids at 21+5 weeks onwards. Some institutions are offering resuscitation 21 weeks onwards; we currently have very limited information to make strong recommendations. Individual institutions should consider determining the gestational age cutoff to provide resuscitation based on the local settings.

**The optimal timing of ANS should be achieved by a more accurate prediction of preterm birth rather than a routine strategy of repeat dosing, which does not improve mortality but may negatively impact fetal brain growth.

***SOGC Canada recommends Ampicillin and/or Erythromycin (alone if allergic to penicillin). For GBS colonized women, Penicillin G/Ampicillin, Cefazolin (non-anaphylactic cefazolin) or Vancomycin (anaphylaxis) prophylaxis, as appropriate, should be considered.

**** Early skin-to-skin care (SSC) should be supported in clinically stable preterm infants, including those <29 weeks' gestation, using a structured transfer process. SSC should not be withheld solely due to concerns regarding IVH.

Table 3: Summary of Enablers with strength of recommendations

Enablers: Any *unit-level practices, behaviours, and cultural elements* that may not directly reduce IVH, but when all team members consistently practice, it improves the quality of care across the entire unit.

Clinical Domain	Practice Element	Strength of Recommendation
Antenatal Care	Arrange in utero transfer to a Level III NICU for pregnancies at risk of delivery at ≤29 weeks' gestation or with an estimated fetal weight ≤1500 g, whenever feasible.	**Strong Recommendation** (moderate certainty of evidence)
Delivery Room Care	In the presence of risk factors* in the infant, send a CBC and Blood culture (minimum 1 mL) and initiate antibiotics (Ampicillin + Gentamicin/Tobramycin) at birth. If the blood culture is positive for pathogenic organisms, treat it appropriately.	Weak recommendation (low to very low certainty of evidence)
	Multicomponent strategy for prevention of postnatal hypothermia (≤36 ^{0}C) and hyperthermia (>38 ^{0}C): (i) prewarmed resuscitation bed with chemical warming mattress activated; (ii) plastic bags and cap; (iii) heated humidified gases for resuscitation;(iv) controllable DR temperature set at ≥23 °C.	**Strong Recommendation** (based on consensus, low to very low certainty of evidence)
	Multicomponent strategy for intubation in DR: (i) Most procedurally adept at performing intubation and presence of neonatologist; (ii) premedication.	Insufficient evidence, but consistency in unit practice may improve overall quality of care.
	Minimally Invasive Surfactant Treatment (MIST) is the recommended method for surfactant administration for spontaneously breathing infants, provided clinicians are experienced with the technique.	Weak recommendation (low to very low certainty of evidence)
Systemic Management	Avoidance of both hypocapnia and hypercarbia [Target 45-55 mm Hg] as well as CO2 fluctuations within the first 72 hours of life is recommended.	Weak recommendation (based on physiological rationale, low to very low certainty of evidence)

	Judicious use of inotropic medications. Investigate the underlying etiology. Avoid inotropes or fluid boluses in the absence of signs of circulatory shock, impaired tissue perfusion (poor pulses or abnormal capillary refill, metabolic acidosis, increased lactate, dropping urine output, or low cerebral saturations if NIRS when used). It is ideal to obtain Targeted neonatal Echo (TnECHO) if available prior to initiating inotropes.	Weak recommendation (based on physiological rationale, low to very low certainty of evidence
Procedural Guideline	Invasive BP monitoring is preferred over manual BP monitoring in the first 72 hours for infants born ≤ 26 weeks (stable) and ≤ 29 weeks (sick)	Insufficient evidence, but consistency in unit practice may improve overall quality of care.
	Multicomponent strategy is recommended, including (i) evaluating and rationalizing bloodwork; (ii) using umbilical lines preferably for bloodwork; (iii) limiting heal lances to avoid pain; (iv) drawing and returning blood slowly from central lines, 1ml per 30 secs.	
	Infusion of all medications slowly, especially fluid boluses of 10 mL/kg or more over a minimum of 30 minutes, is recommended.	
	Avoid prolonged suction > 15 secs and avoid routine suctions. Use closed suction systems on mechanically ventilated infants.	
Minimal Medical Handling	Implement a neuroprotective developmental care bundle that includes: (1) preservation and promotion of parental touch; (2) two-person care for hands-on procedures (one providing containment); (3) individualized care based on infant sleep–wake cycles; and (4) clustering and pre-planning of routine care and assessments.	Insufficient evidence, but consistency in unit practice may improve overall quality of care.
Ambient Light and Noise	Minimize environmental stimulation by reducing bedside noise exposure, including lowering alarm frequency and volume where safe and avoiding nonessential discussions at the bedside. Minimize excessive light exposure by using incubator covers and shielding the infant's eyes during procedures that require bright direct light. Use bedside signage to support team awareness and adherence to these practices.	Insufficient evidence, but consistency in unit practice may improve overall quality of care.

*Risk factors include positive maternal blood culture, maternal fever > 38^0C, rupture of membrane > 18 hours, foul-smelling amniotic fluid, maternal/fetal tachycardia or leucocytosis

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The following practices are frequently included in neuroprotective care bundles, but there is insufficient evidence to support or refute their independent effectiveness in reducing IVH, hence no recommendations can be made at current times.

Clinical Domain	Practice Elements	Strength of Recommendation
Systemic Management	The infusion of base (Sodium bicarbonate or THAM) within the first 72 hours of life is recommended. [Accept pH>7.20]	Insufficient evidence
	Early targeted treatment of predominantly left-to-right shunting Patent Ductus Arteriosus with a diameter ≥ 1.5 mm within ≤ 72 hours of birth.	Insufficient evidence. Recent literature shows a signal towards harm.
	Risk-based indomethacin prophylaxis in selective cases at a high risk of severe IVH (such as lack of antenatal corticosteroids, male sex, GA ≤ 26 weeks at birth, intubated > 24 hours of life).	Insufficient evidence
Head and Body Positioning	Use developmental positioning strategies to support physiologic stability in preterm infants, including the use of positioning aids to maintain flexion, avoiding sudden changes in posture, and providing gentle but firm containment during handling. There is insufficient evidence to recommend routine midline positioning specifically for IVH prevention. Prone positioning may be used selectively for clinical benefit (e.g., respiratory support) with appropriate monitoring. Skin-to-skin care should not be deferred solely for positioning considerations.	Insufficient evidence to recommend any specific positioning strategy

Appendix 1: Summary of Evidence

Intervention	Summary of Evidence
Offer Antenatal Steroids to women at risk of preterm birth within 7 days at or beyond 22 weeks of gestation, where active resuscitation is planned.	Meta-analysis of data from 9 trials (n = 4368) showed the full course of ANS is associated with a slight reduction in severe IVH risk (Any corticosteroid 1.3% versus Placebo 2.6%, RR, 0.54 [95%CI, 0.35-0.82]; NNT, 80 [95%CI, 48-232]). The infants between 22-24 weeks of gestational age were not included in the previous trials but given the strong evidence of benefit in >24 weeks infants, the recommendation is based on scientific rationale in any infant receiving active resuscitation at birth. [1,2]
Maximum survival benefit of Antenatal Steroids peaks at 12 hours and continues till 14days of birth, but no differential impact of timing of steroids on the risk of IVH.	Neonates exposed to ANS 2 to 7 days before delivery were the least likely to develop respiratory distress syndrome (51.3%), compared to those receiving ANS <2 days, 7 to <14 days, and ≥14 days before delivery (62.7%, 55.9%, and 57.6%, respectively, p<0.001). Adjusted OR for infant survival without major neonatal morbidity [IVH ≥3, NEC, PVL, ROP] was lower in infants exposed to ANS < 24h before birth (OR = 0.65; 95% CI = 0.39-1.08), ANS 24-47h (OR = 0.67; 95% CI = 0.35-1.29), ANS > 7 days (OR = 0.59; 95% CI = 0.35-1.02) compared to ANS 48h – 7 days (reference). [No statistical significance]. Adjusted for maternal smoking, maternal blood pressure disease, placenta previa, placental abruption, PPROM, regionalization of care, gestational age, SGA, infant gender and surfactant therapy within 2 h after birth. Significant differences were found in anthropometrics including lower birth weight, shorter length, and smaller head circumferences in those born within the window (<7 days) compared with those outside the window (>7 days). Derangements in glucose homeostasis requiring treatment and elevations of thyroid stimulating hormone (TSH) were seen in infants born outside the ideal therapeutic window. [3-5] Recently, In a cohort of neonates born in Canada from 23 to 31 weeks' gestation, ANS administration was associated with a reduction in neonatal mortality as early as 2 hours after the administration of the first dose. The interval associated with the greatest reduction in neonatal mortality was between 12 hours and 14 days before birth, which was wider than the currently accepted optimal interval of 1 to 7 days. [6]
Administer intrapartum prophylaxis for threatened preterm labour with unknown Group B streptococcus status or positive Group B streptococcus swab, ideally > 4 hours before birth.	Preterm prelabour rupture of the membranes and preterm labour are associated with early-onset neonatal infection. Meta-analysis of 4 trials (n = 893) showed a small reduction in severe IVH (RR, 0.73 [95%CI, 0.42-1.26], not statistically significant). [1,7]
Offer magnesium sulphate for fetal neuroprotection to women at risk of	Meta-analysis of data from 6 trials (n = 4559) showed Magnesium sulphate used for neuroprotection or tocolysis is associated with negligible reduction in severe IVH risk (RR, 0.80 [95%CI, 0.61-1.06], not statistically significant).

imminent preterm birth. At the threshold of viability, use should be individualized and linked to a plan for active neonatal resuscitation.	Cochrane review reported reduced severe IVH (grade 3 or 4) (RR 0.76, 95% CI 0.60 to 0.98; 5 RCTs, 5885 infants; NNT 92, 95% CI 55 to 1102). *Notes: Given < 24h before birth, less than 32 weeks' gestation reduces the risk of cerebral palsy (RR 0.71, 95% CI 0.57 to 0.89; 6 RCTs, 6107 children; NNT 60, 95% CI 41 to 158), and there is limited evidence of similar effects in <24 weeks.*[1,8]
Allow deferred cord clamping for 60 seconds in vigorous preterm infants when feasible. Cord milking in infants <28 weeks' gestation is not recommended.	Meta-analysis of 15 trials (n = 2501) showed a negligible reduction in the risk of severe IVH (RR 0.96 [95% CI 0.65-1.42], not statistically significant, moderate certainty.[1] Meta-analysis of 6 trials (n = 866) showed an increase in the risk of severe IVH (RR 1.82 [95% CI 1.03-3.21] with umbilical cord milking compared to deferred cord clamping. [1] A Cochrane review reported that DCC may make little or no difference to the number of babies with severe IVH (RR 0.94, 95% CI 0.63 to 1.39, 10 studies, 2058 babies, low certainty) but slightly reduces the number of babies with any grade IVH (RR 0.83, 95% CI 0.70 to 0.99, 15 studies, 2333 babies, high certainty).[9] One RCT (n = 150) compared delayed cord clamping with respiratory support versus without respiratory support, no significant differences in the incidences of any IVH (RR 1.50, 95% CI 0.65 to 3.46) and severe IVH (RR 1.33, 95% CI 0.31 to 5.75), with low certainty of evidence.[10] Recent meta-analysis and individual participant data suggests high certainty of evidence that the long DCC (> 120 secs) improves survival, in all gestational age subgroups and low certainty of evidence that none of the umbilical cord management strategies impacts the incidence of IVH (any grade). All cord management strategies compared head-to-head, failed to show a difference in IVH rates, < 28 weeks in under-represented, high risk of bias in studies ICS/PBCC is under-represented. Long DCC is associated with the risk of hypothermia. [11-13]
Non-invasive respiratory support (e.g., CPAP) is recommended as the primary mode of respiratory support for spontaneously breathing preterm infants born at ≥24 weeks' gestation.	Meta-analyses of RCTs suggest benefit in composite of Death/BPD without any increase in severe IVH [OR 1.1 (0.84 to 1.44)]. This practice is also endorsed by the 2026 European RDS guidelines.[14] The ideal practice for neonates <25 weeks in less certain, as these patients have not yet been represented in RCTs. Recent cohort studies show conflicting results in relation to brain injury when comparing initial non-invasive vs. invasive respiratory support. Among preterm infants 22-24 weeks GA (n = 230), severe IVH or death by 36 weeks' PMA was lower in the invasive respiratory support within the first 10 mins of birth group (adjusted OR 2.20; 95% CI, 1.07-4.51; *p* =0.03). In a large Chinese cohort, the practices associated with severe IVH in 24-32 weeks infants were intubation at birth (Adjusted OR 1.15, 95% CI 1.01-1.32), receiving initial invasive respiratory support (Adjusted OR 2.50, 95% CI 2.20-2.83), requiring surfactant (Adjusted OR 2.15, 95% CI 1.83-2.53) [15-17]

If using a conventional form of mechanical ventilation, volume-targeted ventilation (VTV) as an adjunct is recommended in the first 72 hours of life	VTV protects from volutrauma that may result from inadvertent and unnecessarily high tidal volumes during the dynamic phase of respiratory physiology in the 1st 72 hours. A Cochrane Review (2017) [10 RCTs (n = 712)] reported that VTV decreases the risk of Severe IVH by (RR 0.53, 95% CI 0.37 to 0.77; NNT 11, 95% CI 7 to 25). In addition, it decreases the risk of pneumothorax by (RR 0.52, 95% CI 0.31 to 0.87; NNT 20) and hypocarbia (RR 0.49, 95% CI 0.33 to 0.72; NNTB 3). A recent meta-analysis reported 13 RCTs (n = 878) VTV compared to pressure-limited ventilation, reduced the risk of severe IVH [RR 0.51 (95% CI 0.36-0.72), low certainty]. European Consensus Guidelines on the Management of Respiratory Distress Syndrome,2025 cites the Cochrane evidence base for volume-targeted rather than pressure-limited ventilation in neonates and includes recent evidence on early VTV in extremely preterm infants.[18] There is no evidence that elective High-frequency oscillatory ventilation or High-frequency jet ventilation, compared to conventional ventilation, reduces the risk of IVH. [Elective HFOV vs CMV, 19 RCTs, n= 4196, RR= 1.11 (95% CI 0.96-1.29) moderate certainty, Elective HFJV vs CMV, 2 RCTs, n=193, RR= 1.37 (95% CI 0.79-2.37), low certainty]. [1,19]
Intravascular Vitamin K (0.5 mg) is recommended	A Cochrane review (2018) reported no eligible trials. One study compared IV to IM vitamin K and compared various dosages of vitamin K (quality of the evidence for the outcomes evaluated as low). There was no statistically significant difference in vitamin K levels in the 0.2 mg IV group compared to the infants receiving either 0.2 or 0.5 mg vitamin K IM (control) on day 5. By day 25, vitamin K_1 levels had declined in all groups, but infants who received 0.5 mg vitamin K IM had higher levels of vitamin K_1 than either the 0.2 mg IV or the 0.2 mg IM group. Day 5 vitamin K_1 levels and vitamin K_1O levels were significantly lower in the 0.2 mg IM group when compared to the 0.5 mg IM group. On day 25, vitamin K_1O and K1 levels were not significantly different in the 0.2 mg IM groups and the 0.5 mg IM groups. Two QI studies report efficacy in reducing IVH when this approach is used as an element of the care bundle. [20,21]
Encourage EARLY skin-to-skin care using a two-person transfer process. If skin-to-skin care is not feasible, encourage positive parental touch such as hand hugging/containment. Involve parents in facilitated tucking and calming during routine care and painful procedures. The need for minimal	Rationale: Parental involvement is comforting and essential to balance all negative sensory stimuli in the intensive care environment. There is a lack of studies that investigate the direct impact of parental involvement in care on the risk of IVH. As stated above, there is very low certainty of evidence that minimal handling during the first 72 hours of life significantly reduces the risk of IVH. <u>Therefore, the benefits of skin-to-skin care within 72 hours, should not be deferred in the context of minimal handling.</u> Strong evidence from RCT, pragmatic clinical studies, and population-based registry data supports early skin-to-skin care (SSC) as beneficial and feasible for preterm infants. Randomized trial data in very preterm infants show that delivery-room SSC is safe and feasible, without adverse effects on physiological stability, and later follow-up found improved breastfeeding outcomes, supporting SSC as a low-cost intervention that should be encouraged in clinical practice. Population-based registry data from the Swedish Neonatal Quality Register further show that early SSC in extremely and very preterm infants is not associated with increased

handling should not, by itself, preclude skin-to-skin care.	intraventricular hemorrhage (IVH) or sepsis. In parallel, contextual evidence from quality-improvement studies suggests that brain-protective care bundles emphasizing minimal handling / minimal stimulation are associated with lower severe IVH rates in very preterm populations. Taken together, the direct evidence supporting SSC, along with the absence of increased IVH risk in feasibility and registry studies, outweighs indirect concerns extrapolated from minimal-handling practices; therefore, SSC should be strongly advocated for, using a careful two-person transfer process and individualized clinical judgment.[22-28] Why this is a Strong recommendation despite moderate certainty • Benefits clearly outweigh harms • Neurodevelopmental, bonding, and breastfeeding benefits • No evidence of increased IVH risk • High value placed by families • Low cost and high feasibility • Consistent international practice trends

Enablers	Summary of Evidence
Arrange in utero transfer to a Level III NICU for pregnancies at risk of delivery at ≤29 weeks' gestation or with an estimated fetal weight ≤1500 g, whenever feasible.	Transported infants had a significantly higher risk of severe (grade III/IV) IVH compared with inborn infants < 28 weeks GA (Inborn 5.8% and Outborn 9.7%, adjusted OR 1.83; 95% CI, 1.03-3.21). Adjusted for gender, GA, BW, mode of delivery, IUGR, maternal infection, antepartum hemorrhage, maternal recreational drug use, intubation at birth, surfactant administration, chest compressions at birth, delivery room adrenaline, Apgar scores, and inotropes.[29-31]
In the presence of risk factors in the infant, send a CBC and Blood culture (minimum 1 mL) and initiate antibiotics (Ampicillin + Gentamicin/Tobramycin) at birth. If the blood culture is positive for pathogenic organisms, treat it appropriately.	Risk factors include preterm labour, preterm premature rupture of membranes (PPROM), suspected chorioamnionitis, and maternal sepsis. The approach is based on early-onset sepsis guidelines [EPIQ bundle]. A small cohort study (n = 274) reported that CSF collection within 72 hours of life increased the odds of IVH of any grade by fourfold. Postponing CSF sampling beyond 72 hours, when used with other bundle elements, reduced the incidence of IVH from 41% to 29%.[32]
Multicomponent strategy for prevention of postnatal hypothermia (≤36 ^{0}C) and hyperthermia (>38 ^{0}C): (i) prewarmed resuscitation bed with chemical warming mattress activated; (ii) plastic bags and cap; (iii) heated humidified gases for resuscitation;(iv) controllable DR temperature set at ≥23 °C.	A meta-analysis of 4 RCTs showed that interventions like plastic bags and thermal mattresses individually did not affect IVH rates, but heated humidified gases [2 RCT] reduced the risk of IVH > grade 2, 0.39 [0.17-0.91]. Cohort studies (QI studies) have reported conflicting results. [33-36]
Multicomponent strategy for intubation in DR: (i) Most procedurally adept at performing	Individual elements have not been tested in well-designed studies. Single-center quality improvement studies have reported using various combinations of these elements in their

intubation and presence of neonatologist; (ii) premedication.	center-specific bundles. QI studies have inherent biases resulting in very low certainty of evidence. [37-39]
Minimally Invasive Surfactant Treatment (MIST) is the recommended method for surfactant delivery for spontaneously breathing infants, provided clinicians are experienced with the technique.	A meta-analysis reported that compared to invasive ventilation in infants <33 weeks of GA, LISA had lower odds of severe IVH [OR 0.44, 95% CI 0.19-0.99, absolute RD 58 fewer per 1000 infants].[16] When LISA is compared to INSURE [6 RCTs], the reduction in severe IVH was not statistically significant [RR 0.79, 95% CI 0.52-1.20], with low certainty of evidence.[1] It should be noted most RCTs included in meta-analyses comprise of patients >25 weeks. Kribs et al conducted an RCT (n=211) of patients 23-26 and found a lower risk of severe IVH with LISA. Cohort studies from the German and Canadian Neonatal Networks that include neonates <27 weeks have also shown lower risk of IVH/brain injury in babies. [1,16,40]
Invasive BP monitoring is preferred over manual BP monitoring in the first 72 hours for infants born < 26 weeks (stable) and < 29 weeks (sick)	Physiological rationale: Manual BP measurements may induce discomfort, resulting in fluctuations in cerebral blood flow. Two QI studies have included this as one of the elements in the care bundle. However, due to the limitations of the QI design, it is impossible to ascribe the bundle's efficacy to individual elements. [20]
Multicomponent strategy is recommended, including (i) evaluating and rationalizing bloodwork; (ii) using umbilical lines preferably for bloodwork; (iii) limiting heal lances to avoid pain; (iv) drawing and returning blood slowly from central lines, 1ml per 30 secs.	Physiological rationale: Less disturbance will result in fewer fluctuations in cerebral blood flow.[20]
Infusion of all medications slowly, especially fluid boluses of 10 mL or more over a minimum of 30 minutes, is recommended.	Physiological rationale: Less disturbance will result in fewer fluctuations in cerebral blood flow. Few QI studies have included this as an element in the care bundle. However, due to the limitations of the QI design, it is impossible to ascribe the bundle's efficacy to individual elements.[20]
Avoid prolonged suction < 15 secs and avoid routine suctions. Use closed suction systems on mechanically ventilated infants.	Physiological rationale: It prevents rapid fluctuations in cerebral blood flow. QI studies report it as an element of the bundle. No data were found to establish a link between suctioning and IVH. However, it is well documented that changes occur in blood pressure, cerebral blood flow, and intracranial pressure during suctioning. [41-43]
Avoidance of both hypocapnia and hypercarbia [Target 45-55 mm Hg] as well as CO2 fluctuations within the first 72 hours of life is recommended.	Physiological rationale: Prevents rapid fluctuations in cerebral blood flow. Three single-center QI studies report it as an element of the bundle. *Canadian Pediatric Society guidelines [2019] Permissive hypercapnia: A meta-analysis concluded that permissive hypercapnia did not have notable effects on IVH in extremely LBW infants. A Cochrane review (2001) included 2

	RCTs that concluded that evidence did not support the use of permissive hypercapnia to prevent morbidity and mortality, severe IVH and PVL. Cohort studies have conflicting reports. Hypocapnia: No data exists to support that avoidance of hypocapnia reduces the risk of IVH. For hypocapnia, reported parameters for CP (pCO2 <35 mmHg) and PVL (PaCO2 <35.0 mmHg) were identified. [20,44,45]
Judicious use of inotropic medications. Investigate the underlying etiology. Avoid inotropes or fluid boluses in the absence of signs of circulatory shock, impaired tissue perfusion (poor pulses or abnormal capillary refill, metabolic acidosis, increased lactate, dropping urine output, or low cerebral saturations if NIRS when used). It is ideal to obtain Targeted neonatal Echo (TnECHO) if available prior to initiating inotropes.	Four QI studies report efficacy in reducing IVH when this approach is used as an element of the care bundle. The relationship of IVH to hypotension or hypertension is not well established, but multiple studies have implicated these as causal factors. In general, the evidence supports cautious treatment; clinical findings and standard numeric parameters should be determinants of therapy. [20,38] [Target BP according to Blood pressure assessment guidelines, EPIQ bundles version June 2022]
Implement a neuroprotective developmental care bundle that includes: (1) preservation and promotion of parental touch; (2) two-person care for hands-on procedures (one providing containment); (3) individualized care based on infant sleep–wake cycles; and (4) clustering and pre-planning of routine care and assessments.	Some QI studies have included this as an element in the care bundle. However, due to the limitations of the QI design, it is impossible to ascribe the bundle's efficacy to individual components.[20] Developmental care practices that minimize stress and handling are widely recommended as part of neuroprotective care for extremely preterm infants. The Canadian Paediatric Society position statement on neuroprotection supports minimizing handling, clustering care, and promoting parental involvement and containment strategies to reduce fluctuations in cerebral blood flow, which are implicated in the pathogenesis of IVH. Evidence from quality improvement initiatives demonstrates that implementation of structured care bundles—including minimal medical handling, two-person care, clustering of interventions, and positioning/containment—has been associated with sustained reductions in severe IVH rates in very preterm populations.[46,47] In parallel, randomized and pragmatic studies of family-integrated care models, such as the Family Integrated Care Trial, show that increased parental involvement and touch improve infant and parent outcomes without harm, supporting the inclusion of parental touch as a core component of care. Although the evidence linking individual components of developmental care directly to IVH reduction is of low-to-moderate certainty due to the multifactorial nature of interventions, the consistency of findings across observational, physiologic, and interventional studies, combined with a strong biological rationale and minimal risk, supports implementation of

	these practices as part of a comprehensive neuroprotective strategy.
Minimize environmental stimulation by reducing bedside noise exposure, including lowering alarm frequency and volume where safe and avoiding nonessential discussions at the bedside. Minimize excessive light exposure by using incubator covers and shielding the infant's eyes during procedures that require bright direct light. Use bedside signage to support team awareness and adherence to these practices.	The physiologic rationale is that reducing environmental disturbance may help limit stress-related fluctuations in systemic and cerebral hemodynamics. Although several IVH-prevention quality-improvement bundles have included noise and light reduction as part of a broader brain-protection strategy, the available data do not allow the independent effect of these individual bundle elements to be determined.[20,48]
The infusion of base (Sodium bicarbonate or THAM) within the first 72 hours of life is recommended. [Accept pH>7.20]	Although the use of bicarbonate for metabolic acidosis is widespread, there is little evidence of its efficacy and a vast body of literature on its side effects [transient paradoxical worsening of intracellular acidosis, loss of cerebral vascular autoregulation, decreased cerebral blood flow and acute changes in cerebrospinal fluid pH]. If necessary, slowly diluting the bicarbonate and infusing it is preferable to rapidly concentrated infusions. Treatment of the underlying etiology is recommended instead of treatment of metabolic acidosis itself with NaHCO3. One RCT (1977) did not find a statistically significant difference in the incidence of IVH with base infusion vs no treatment, RR 1.24 (95% CI 0.47-3.28). Three QI studies report efficacy in reducing IVH when this approach is used as an element of the care bundle. [20]
Early targeted treatment of predominantly left-to-right shunting Patent Ductus Arteriosus with a diameter ≥ 1.5 mm within < 72 hours of birth.	Early left-to-right shunting through a PDA may alter cerebral hemodynamics and has been hypothesized to contribute to hypoxia–reperfusion injury in extremely preterm infants.[49] Observational data suggests that using early hemodynamic screening and selective treatment strategies are associated with lower rates of severe IVH (7% vs 27%, p<0.001). [50] Only 1 RCT of early indomethacin vs placebo had death or abnormal head ultrasound as the primary outcome. This trial was terminated early due to lack of indomethacin availability, however showed significantly less pulmonary hemorrhage (2% vs 21%, p=0.004) and a non-significant trend towards less IVH (4.5% vs, 12.5%, p=0.21). None of the other trials of early targeted PDA treatment involved IVH as a primary outcome and did not demonstrate reduction in IVH with early treatment vs expectant management (BeNeDuctus Trial [54 (39.4) vs 51(37.5%) RR 0.95 (0.71 to 1.29)for all IVH and 9 (6.6) vs 11 (8.1) RR 1.23 (0.53 to 2.88)for severe IVH][51], Baby-OSCAR trial 34 (10.6) vs 45

	(13.9), 1.30 (0.93–1.82) for severe IVH). [52] A Cochrane review of very early (< 3 days) treatment vs expectant management showed no difference in IVH all grades severe IVH (RR 0.91, 95% CI 0.34 to 2.48, 3 RCTs, n = 234) and severe IVH]. [53,54] Therefore, there is currently insufficient evidence from high-quality randomized controlled trials to recommend early targeted PDA treatment for prevention of IVH.
Risk-based indomethacin prophylaxis in selective cases at a high risk of severe IVH (such as lack of antenatal corticosteroids, male sex, GA < 26 weeks at birth, intubated > 24 hours of life) is recommended.	A Cochrane review (2023)of reviews specifically reported the impact of prophylactic indomethacin on the risk of severe IVH (5 reviews) reported : (i) prophylactic indomethacin vs placebo reduced severe IVH [RR 0.66, 95% CI 0.53-0.82; 14 RCTs, N = 2588]; (ii) prophylactic ibuprofen possibly reduced severe IVH [RR 0.67, 95% CI 0.45-1.00; 7 RCTs, n = 925]; No evidence of difference for prophylactic acetaminophen and surgical PDA ligation. Four reviews reported on the outcome of any grade IVH (grades I to IV): (i) prophylactic indomethacin versus placebo: reduced all grades of IVH [RR 0.88, 95% CI 0.80 - 0.98; 14 RCTs, n = 2532]. (ii) prophylactic ibuprofen versus placebo: no evidence of a difference [RR 0.96, 95% CI 0.78 to 1.17; 6 RCTs, n = 901]. Another meta-analysis (2023) reported similar results in prophylactic indomethacin [15 RCTs, RR 0.64 (0.52-0.79), moderate certainty] and prophylactic ibuprofen [8 RCTs, RR 0.68(0.46-1.01), low certainty]. [1,20,55] Prophylactic indomethacin has been shown in multiple randomized controlled trials and meta-analyses to reduce the incidence of severe IVH in extremely preterm infants. However, it has not consistently improved long-term neurodevelopmental outcomes or survival, which limits the strength of recommendation. The Cochrane review demonstrated that prophylactic indomethacin significantly reduces severe IVH but does not improve mortality or long-term neurodevelopment, supporting moderate certainty of evidence for short-term outcomes. In addition, secondary analyses (e.g., TIPP trial) suggest that the benefit of indomethacin may be greater in high-risk subgroups, including infants with lower gestational age and higher illness severity. Given the balance of benefits (reduction in severe IVH) and uncertainties (no clear long-term benefit, potential renal and gastrointestinal side effects), a targeted, risk-based approach is reasonable rather than universal prophylaxis. But the clear structure of “risk-based approach” is yet to be defined. There is insufficient evidence to select patients who will benefit from the intervention.
Use developmental positioning strategies to support physiologic stability in preterm infants, including the use of positioning	Physiological rationale: 90-degree head rotation and Trendelenburg position cause jugular vein obstruction and congestion of the jugular venous-venule drainage system, increasing the risk of IVH and should be avoided.

aids to maintain flexion, avoiding sudden changes in posture, and providing gentle but firm containment during handling. There is insufficient evidence to recommend routine midline positioning specifically for IVH prevention. Prone positioning may be used selectively for clinical benefit (e.g., respiratory support) with appropriate monitoring. Skin-to-skin care should not be deferred solely for positioning considerations.	Most QI studies have included this as one of the elements in the care bundle. However, due to the limitations of the QI design, it is impossible to ascribe the bundle's efficacy to individual elements. A meta-analysis of 3 RCTs summarised that when comparing supine head midline to supine head rotated (n = 290), there is no evidence of a difference in the risk of severe IVH [RR 0.71 (95% CI 0.37-1.33)]. A small RCT (N = 180) suggested that head-end elevation to 30 degrees may likely reduce the risk of severe IVH.[1,20] Systematic reviews of IVH-prevention bundles note that while positioning (including midline head positioning) is frequently included, the independent effect of individual elements cannot be determined due to the multifactorial nature of interventions. Similarly, there is no high-quality evidence demonstrating that routine midline positioning alone reduces IVH incidence. Prone positioning may confer benefits in selected contexts, particularly for improving oxygenation and respiratory mechanics in preterm infants, but it should be used with appropriate monitoring and not as a primary neuroprotective intervention. Importantly, there is no evidence to support withholding skin-to-skin care (SSC) due to positioning concerns; SSC has independent evidence of benefit and safety and should be prioritized when feasible.

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