Intervention	Summary of Findings	Citations

Pre-Delivery Interventions	• **Pre-delivery interventions** to reduce IVH risk:
	  • Antenatal betamethasone
	  • Antenatal magnesium
	  • Delivery in a tertiary care center
	• **ACOG recommendations**:
	  • Corticosteroids for mothers at risk of preterm delivery **24 0/7 – 33 6/7 weeks**
	  • Consider corticosteroids **34 0/7 – 36 6/7 weeks**
	  • Magnesium sulfate for fetal neuroprotection if **imminent delivery <34 weeks**
		- Brownfoot, F. C., Gagliardi, D. I., Bain, E., Middleton, P. & Crowther, C. A. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* vol. 2013
		- Doyle, L. W., Crowther, C. A., Middleton, P., Marret, S. & Rouse, D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database of Systematic Review.*
		- Carteaux, P. *et al.* Evaluation and development of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics* **111**, (2003).
		- El-Sayed, Y. Y., Borders, A. E. B. & Gyamfi-Bannerman, C. Antenatal Corticosteroid Therapy for Fetal Maturation. *Obstetrics and Gynecology* **130**, (2017).

Delivery & Golden Hour Interventions	• Delayed cord clamping should be employed when possible – some studies show possible benefit in delayed cord clamping in non-vigorous infants by allowing for resuscitation before cord clamping, but evidence does not currently support this practice • Umbilical cord milking should be avoided in preterm infants because rapid fluctuations in cerebral blood flow and increased vascular fragility in the immature brain significantly raise the risk of severe intraventricular hemorrhage. • Avoid cold stress – decreasing incidence of hypothermia in VLBW infants has shown to decrease incidence of IVH	- Katheria, A. *et al.* Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm - Seidler, A. L. New evidence on physiological-based cord clamping at preterm birth: balancing potential benefits and risks. *The Lancet Regional Health - Europe* vol. 48 Trial. *JAMA Netw Open* **7**, E2411140 (2024). - Miller, S. S., Lee, H. C. & Gould, J. B. Hypothermia in very low birth weight infants: Distribution, risk factors and outcomes. *Journal of Perinatology* **31**, (2011).
Fluid management & avoiding hypernatremia	• Severe dehydration & hypoperfusion can result in decreased cerebral perfusion = increased rates of IVH	- Lee, H. J. *et al.* Early sodium and fluid intake and severe intraventricular hemorrhage in extremely low birth weight infants. *J Korean Med Sci* **30**, 283–289 (2015). - Späth, C., Sjöström, E. S., Ahlsson, F., Ågren, J. & Domellöf, M. Sodium supply influences plasma

	• Highest risk of IVH associated with hypernatremia appears to be present in infants requiring transfusions of NS boluses and blood products (increased when Na+ intake exceeds 3mEq/kg/day)	sodium concentration and the risks of hyper-and hyponatremia in extremely preterm infants. *Pediatr Res* **81**, 455–460 (2017).
Avoiding hypotension & hypertension	• Hypotension and hypertension are associated with severe IVH • Evidence suggest that *physiologic hypotension* in well-perfused preterm infants without evidence of end-organ malperfusion (low UOP, changes in creatinine, hypoperfusion, etc.) is **safe** • Early inotrope use in extremely preterm infants is associated with increased cerebral blood flow (which can cause IVH), severe brain damage, and death • Recommended to correct hypotension in infants with signs of malperfusion first with a slow normal saline bolus, then resort to pressors ONLY if volume correction has not succeeded	- Vesoulis, Z. A. *et al.* Blood pressure extremes and severe IVH in preterm infants. *Pediatr Res* **87**, 69–73 (2020). - Perlman, J. M., Cilio, M. R. & Polin, R. A. *Neurology: Neonatology Questions and Controversies*. *Neurology: Neonatology Questions and Controversies* (2018). - Dempsey, E. M., Al Hazzani, F. & Barrington, K. J. Permissive hypotension in the extremely low birthweight infant with signs of good perfusion. *Arch Dis Child Fetal Neonatal Ed* **94**, (2009).

Neonatal respiratory management for IVH prevention	• Volume-targeted ventilation is associated with significant reduction in the risk of IVH
	• Hypercarbia and hypocarbia, which impact cerebral blood flow, in the first 4 days of life increases risk of severe IVH
	• Surfactant administration methods affect impact on IVH rates:
	  • In-and-out surfactant administration (INSURE) = decreased rate of IVH compared with standard intubation for surfactant administration
	  • Less Invasive Surfactant Administration (LISA) is associated with decreased IVH risk compared to INSURE
	• Intubation is a noxious procedure = increases HR & BP, which in turn increases cerebral blood flow
	  • IVH risk is even higher with intubation in the DR & multiple intubation attempts
	• Evidence does not support delaying extubation in extremely preterm infants in the IVH window!
		- Klingenberg, C., Wheeler, K. I., Mccallion, N., Morley, C. J. & Davis, P. G. Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Database of Systematic Reviews* vol. 2017
		- Kim, S. Y., Lim, J. & Shim, G. H. Comparison of mortality and short-term outcomes between classic, intubation-surfactant-extubation, and less invasive surfactant administration methods of surfactant replacement therapy. *Front Pediatr* **11**, (2023).
		- Danan, C. *et al.* A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants. *Pediatr Pulmonol* **43**, (2008).
		- Mukerji, A. *et al.* Early versus delayed extubation in extremely preterm neonates: a retrospective cohort study. *Journal of Perinatology* **40**, (2020).

Avoiding noxious stimuli	• Most data on benefits of minimum stimulation (avoiding noxious stimuli) demonstrates benefits in neurodevelopmental outcome; however, there is a theoretical benefit in reduction of stimuli, which may lead to decreased fluctuations in cerebral blood flow. • Preterm infants have limited autonomic regulation, making them vulnerable to elevated sound levels that disrupt BP, oxygenation, respiratory rate, and sleep • Irritating odors show cortical hemodynamic modifications similar to a pain response in preterm infants, while olfactory stimulation with breast milk can stabilize vitals and reduce pain response.	- Bartocci, M., Winberg, J., Papendieck, G. *et al.* Cerebral Hemodynamic Response to Unpleasant Odors in the Preterm Newborn Measured by Near-Infrared Spectroscopy. *Pediatr Res* 50, 324–330 (2001). - Benlamri, A. *et al.* Neuroprotection care bundle implementation is associated with improved long-term neurodevelopmental outcomes in extremely premature infants. *Journal of Perinatology* 42, (2022). - Parra J, de Suremain A, Berne Audeoud F, Ego A, Debillon T. Sound levels in a neonatal intensive care unit significantly exceeded recommendations, especially inside incubators. Acta Paediatr. 2017 Dec;106(12):1909-1914.
Neutral & midline head positioning	• Improper positioning of the head can impede venous jugular drainage and decreased cerebral perfusion. • Neutral/midline head positioning is included in the most successful IVH prevention bundles • Literature has shown an uncertain benefit of neutral/midline head positioning; Cochrane review shows no reduction in IVH incidence, but some benefit in IVH mortality	- Pellicer, A., Gayá, F., Madero, R., Quero, J. & Cabañas, F. Noninvasive continuous monitoring of the effects of head position on brain hemodynamics in ventilated infants. *Pediatrics* 109, (2002). - Mohamammadie, Z. R., Ramezani, M., Heidarzadeh, M., Sezavar, M. & Saki, A. The effect of head positioning on brain tissue oxygenation in preterm infants: a randomized clinical trial study. *Journal of Perinatology* 42. - Romantsik, O., Calevo, M. G. & Bruschettini, M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular haemorrhage in preterm infants. *Cochrane Database of Systematic Reviews* 2020, (2020).
Early skin-to-skin	• Early initiation of skin-to-skin reduces all-cause mortality (sepsis/infection, hypothermia, and apnea), and shows additional benefits in neurodevelopment, pain control, infant stability, bonding, and breastfeeding. • Single study shows no increase in severe IVH when introducing skin-to-skin within the first 72hrs in infants born <28 weeks and <1000g (Minot et al), more studies are needed to full evaluate the balance of risks and benefits in this age group.	- Catherine, ZG, et al. Skin-to-skin contact with an umbilical venous catheter: prospective evaluation in a level 3 unit. *Eur J Pediatr* **175**, (2016). - Immediate “Kangaroo Mother Care” and Survival of Infants with Low Birth Weight. *New England Journal of Medicine* 384, (2021). - Minot KL, Kramer KP, Butler C, Foster M, Gregory C, Haynes K, Lagon C, Mason A, Wynn S, Rogers EE, Liebowitz MC. Increasing Early Skin-to-Skin in Extremely Low Birth Weight Infants. Neonatal Netw. 2021 Jul 1;40(4):242-250