ORIGINAL RESEARCH

A Care-bundle to Prevent Germinal Matrix–Intraventricular Hemorrhage in Neonates

The *LAYA** Group of the Global Newborn Society
**L*ooking *A*t *Y*our practices in *A*pplication

Received on: 01 August 2024; *Accepted on*: 19 September 2024; *Published on*: 30 September 2024

Abstract

Germinal matrix-intraventricular hemorrhages (GM-IVHs) can be seen in up to 25–30% of premature infants. These are associated with a major psychological, social, and financial challenge for care-providers and families caring for premature infants all over the world. The severity is usually classified based on the location and volume vis-à-vis that of the cerebral ventricles, including (A) Grade I GM-IVHs localized in the germinal matrix; (B and C) Grade II and III hemorrhages occupying less than and more than 50% of the ventricular cavities, respectively; and (D) Grade IV IVHs that extend into the surrounding parenchyma with/without a periventricular hemorrhagic infarction (PVH). Germinal matrix-intraventricular hemorrhages have been associated with impaired neurodevelopment (17.5%), static physical disabilities in cerebral palsy (7–63%), deafness (8.6%), and blindness (2.2%). Considering the complex etiopathogenesis of GM-IVH and the fact that most of these events occur within a temporally-delimited period of the first 72 hours after birth, there is increasing interest in the structured application of 3–5 well-accepted preventive measures as a quality improvement (QI) "care bundle" during the high-risk period. In this article, we have described the evidence on which our GM-IVH bundle is based. We have carefully evaluated antenatal factors such as the history of having received steroids and magnesium sulfate, perinatal measures such as delayed cord clamping, management of thrombocytopenia and/or coagulopathy, and postnatal measures such as maintaining a midline head position, cautious endotracheal suctioning and blood withdrawals, and avoidance of routine flushing of intravenous and arterial lines. Based on the strongest evidence and practice consensus, we have adopted a 4-point bundle to prevent GM-IVH in premature infants: (A) Appropriate neonatal resuscitation with, if possible, delayed cord clamping; (B) Golden-hour care; (C) Gentle care of outborn infants including safe transport and avoiding hemodynamic instability; and (D) if needed, management of perinatal thrombocytopenia and coagulopathy. In the next 3–5 years, we will report compliance and changes in the incidence/severity of GM-IVH at our centers.

Keywords: Antenatal corticosteroids, Delayed cord clamping, Germinal matrix-intraventricular hemorrhage care-bundle, Golden hour, Implementation science, Institute of health care improvement, Neonate, Newborn, Periventricular hemorrhage, Tocolytics.

Newborn (2024): 10.5005/jp-journals-11002-0107

Keypoints

Germinal matrix-intraventricular hemorrhage (GM-IVH) is a well-known co-morbidity and mortality of prematurity, especially in very-low-birth-weight (VLBW) infants.

1. A care bundle is a structured, organized attempt to develop protocols to prevent/alleviate possible major risk factors for a disorder.
2. Germinal matrix-intraventricular hemorrhage is a complex, multifactorial disorder that typically occurs within a temporally-delimited period of the first 72-hours after birth, and therefore, developing a clinical care bundle to mitigate known risk factors is logical to improve neonatal outcomes.
3. In this article, we have proposed a 4-point bundle to prevent GM-IVH in VLBW infants: (A) Appropriate neonatal resuscitation, and if possible, delayed cord clamping; (B) Golden-hour care for inborn infants; (C) Gentle care of out born infants, including safe transport and avoiding hemodynamic instability; and (D) if needed, management of perinatal thrombocytopenia and coagulopathy.

Introduction

Germinal matrix-intraventricular hemorrhage (GM-IVH) is an important cause of morbidity and mortality in extremely premature/very low-birth-weight (VLBW) infants.[1–3] The most important predisposing factors in these patients include the fragility of the premature cerebral vasculature and fluctuations in cerebral blood flow.[3,4] Despite improvements in the overall survival rates, the incidence of moderate-to-severe GM-IVH has remained the same among preterm infants in the last few decades. This might be partially explained by improved neonatal care, with increasing survival of ELBW infants born at 22–24 weeks' gestation.[1,5] Indeed, low gestational age is one of the most important risk factors for developing GM-IVH.[6–8] There are some geographic variations in

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How to cite this article: Ayad AEB, Athalye-Jape G, Jape K, *et al*. A Care-Bundle to Prevent Germinal Matrix–Intraventricular Hemorrhage in Neonates. Newborn 2024;3(3):157–179.

Source of support: Parts of the information in this article were obtained in studies supported by work done during the first 3 years of the NIH grant-supported projects HL124078 and HL133022 (AM).

Conflict of interest: Dr Akhil Maheshwari is associated as the Editor-in-Chief of this journal. This manuscript was subjected to this journal's standard review procedures, where this peer review was handled independently of the Editor-in-Chief and his research group.

the incidence of GM-IVH; globally, population-based studies show the incidence of Grade I–II IVH as ranging between 5 and 19% and Grade III–IV at 5–52% (Europe: 5–52%; North America: 8–22%; Asia: 5–36%; Oceania: 8–13%).[6]

In this paper, we have described how we developed our therapeutic "bundle" to lower the risk of GM-IVH in premature infants.[9–11] As defined by the Institute for Healthcare Improvement (IHI), a therapeutic bundle is the concomitant application of 3–5 evidence-based interventions to improve outcomes in a defined subset of patients.[12–14] Although the development of bundles is always an evolving process with scope for further improvement, it is a major advance in our understanding of the impact of therapeutic interventions. There is a need for a better understanding of the scientific principles, continued compliance, and regular measurements to define/refine these interventions continuously.[9,14–16] This section outlines our efforts to define, evaluate, and refine this care bundle to prevent GM-IVH.

Defining GM-IVH

Germinal matrix-intraventricular hemorrhage signifies bleeding in the brain, primarily in the germinal matrix (GM) and then in the ventricles.[1,17,18] Abraham Towbin first identified it in 1968.[19] Grading systems were developed by Papile et al. in 1978 based on head CT scans, and later, several more classifications were developed; Papile and Volpe's classification is currently the most widely accepted all over the world.[20–22] A IV-grade classification system of GM-IVH based on the location and severity of hemorrhage is used most frequently: (A) Grade I hemorrhages are limited to the GM; (B) Grade II implies extension to lateral ventricles without ventricular dilatation; (C) Grade III indicates ventricular hemorrhage with ventriculomegaly; (D) Grade IV is ventricular hemorrhage with extension into the nearby brain parenchyma.[21] Arbitrarily, grades I-II are considered mild, whereas grades III-IV are considered severe GM-IVH.[23] Classifications based on parasagittal views on cranial sonography include 3 grades of severity: Grade I refers to GMH with no/minimal IVH (<10% of ventricular area); Grade II hemorrhage occupies 10–50% of the lateral ventricles; Grade III occupies >50% of these ventricles, usually with ventricular distention and periventricular echodense areas.[24]

The GM is a highly vascular area with abundant neuronal and glial precursor cells. Unlike other brain regions, the GM shows a high degree of angiogenesis, with immature vessels creating immature vessels. These immature vessels lack pericytes, exhibit immature basal lamina low in fibronectin, with less supporting matrix, and have astrocyte end-feet coverage deficient in glial fibrillary acidic protein (GFAP).[25,26] Consequently, the vasculature in the GM remains very fragile and vulnerable to rupture, with a high risk of hemorrhages. Premature infants also have limited cerebral autoregulation and often show fluctuations in cerebral blood flow due to respiratory or hemodynamic instability. Germinal matrix-intraventricular hemorrhage is associated with high mortality and adverse outcomes such as post-hemorrhagic hydrocephalus, cerebral palsy, epileptiform seizures, severe cognitive delays, and visual and hearing impairments. Many of these affected neonates may initially be asymptomatic and are diagnosed only on routine cranial sonograms. Many studies have evaluated antenatal measures like antenatal steroids, magnesium sulfate, and outreach programs perinatally like golden hour, delayed cord clamping, minimal handling, midline position, a nursing bundle of care, transportation care including in utero-transfer, neuroprotective bundle during transfer like avoiding noise, minimizing vibrations, keeping the head in the midline, and respiratory and hemodynamic management as singular measures. However, recent changes in practice have emphasized the potential value of a care bundle approach.

Defining Care Bundles

Care bundles are powerful tools used in modern medicine. These are formulated by applying evidence-based QI interventions that have been considered/proven beneficial in a specific disease or care process.[9] The IHI introduced the concept of "care bundles" mainly to improve medical care and adherence to evidence-based guidelines in intensive care units (ICUs). In this schema, 3–5 evidence-based or globally-accepted interventions are grouped to address specific aspects of patient care.[14] Unless contraindicated, care bundles are not limited to certain patient populations and are usually focused on correcting specific healthcare issues in one or more facilities. The goals are to improve consistency in treatment measures, adherence to best practices, improve patient safety, reduce complications, and lower healthcare costs, morbidity, and mortality. Healthcare bundles can be tailored for preventive medicine, improved clinical management, and/or to manage acute/chronic complications or sequelae. Even though all QI efforts have not been universally proven clinically useful and effective, the bundled application might show different results as the lack of application of one intervention might reduce the efficacy of another. This article reviewed current information supporting various therapeutic interventions and defined a GM-IVH care bundle.

GM-IVH Care Bundle

We have carefully evaluated antenatal factors such as the history of having received steroids and magnesium sulfate, perinatal measures such as delayed cord clamping, management of thrombocytopenia and/or coagulopathy, and postnatal measures such as maintaining a midline head position, cautious endotracheal suctioning and blood withdrawals, and avoidance of routine flushing of intravenous and arterial lines. Based on the strongest evidence and practice consensus, we have adopted a 4-point bundle to prevent GM-IVH in premature infants (Fig. 1): (A) Appropriate neonatal resuscitation with, if possible, delayed cord clamping; (B) Golden-hour care; (C) Gentle care of inborn and outborn infants including safe transport and avoiding hemodynamic instability; and (D) protocolization of respiratory management. In the next 3–5 years, we will report compliance and changes in the incidence/severity of GM-IVH at our centers.

Here is a detailed review of the most discussed preventive/therapeutic interventions:

- Coordinate perinatal care with obstetricians and outborn measurements:
  - Preterm premature rupture of membranes (PPROM) and chorioamnionitis:

Preterm premature rupture of membranes occurs in 2–3% of all pregnancies and is responsible for >25% of preterm births (PTB).[14,27] The definition of PROM in terms of duration is still debatable, but most centers accept 18 hours of ruptured membrane as a significant risk factor for early-onset infections. Existing information shows PPROM or PTB in earlier pregnancies, use of tobacco, presence of sexually transmitted diseases, and low body mass index (BMI) as risk factors for PPROM.[28,29] The underlying etiology of PROM is often unclear; multiple factors such as maternal age, parity, infections,

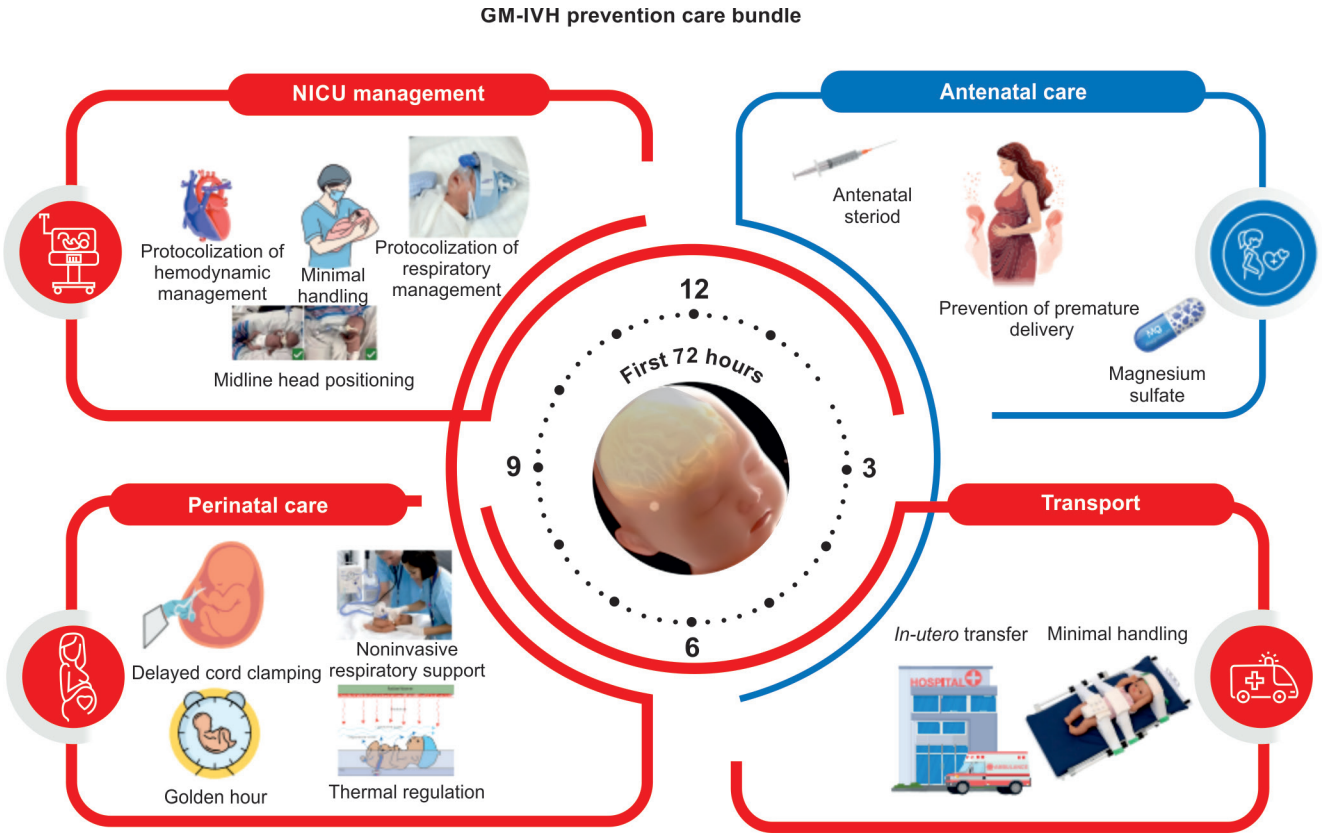


Fig. 1: Measures that are usually considered in developing protocols to prevent GM-IVH. We have selected 4 of these interventions to develop a care bundle: (A) Appropriate neonatal resuscitation with, if possible, delayed cord clamping; (B) Golden-hour care; (C) Gentle care of outborn infants, including safe transport and avoiding hemodynamic instability. The relationship with hemodynamic instability still requires more evidence; (D) Management of perinatal thrombocytopenia (not shown). These steps have been highlighted with red outliners. Several other measures may be helpful, but further evidence is needed

altered structural/functional integrity of the membranes, and genetic factors might be involved.[30,31]

The management of PPROM is usually focused on delaying delivery when possible and optimizing neonatal outcomes. Antibiotics can prolong the duration of pregnancy by preventing chorioamnionitis and consequent/concurrent neonatal infections.[32,33] Broad-spectrum antibiotics are recommended with PPROM as the infection is often polymicrobial and has several microbial agents of chorioamnionitis.[29,34]

Chang et al.[35] compared neonatal morbidity and neurologic outcome at 2 years after birth in a retrospective study of mothers with PPROM who delivered before 32 weeks' gestation and were treated with antibiotics. One hundred sixty-six women were included: 80 were treated with erythromycin and 86 with clarithromycin. The clarithromycin group had a higher median gestational age ($p = 0.005$), but fewer mothers had histopathologically-confirmed chorioamnionitis ($p = 0.004$). After adjusting for the confounding factors, the multivariable analysis showed the incidence of severe IVH (≥ Grade III) was lower in the clarithromycin group (GM-IVH; OR 0.23, 95% CI: 0.06–0.91; also, less BPD; OR 0.34, 95% CI: 0.13–0.90). They suggested that a clarithromycin-based regimen may be worth considering as a choice of erythromycin in PPROM patients.[35,36]

In a retrospective study, Lee et al.[37] compared perinatal outcomes in 314 patients with PPROM who were born at a gestational age <34 weeks and received either an anti-microbial regimen 1 (ampicillin and/or cephalosporins; $n = 195$, 1993–2003) or a regimen 2 (ceftriaxone, clarithromycin, and metronidazole; $n = 119$, 2003–2012). Intra-amniotic infection/inflammation was assessed by a positive amniotic fluid culture and/or an elevated amniotic fluid matrix metalloproteinase-8 (MMP-8) concentrations (>23 ng/mL). Germinal matrix-intraventricular hemorrhages and cerebral palsy (CP) were significantly lower in patients allocated to regimen 2 than regimen 1 (GM-IVH: 2.1 vs 19%, $p < 0.001$ and CP: 0 vs 5.7%, $p < 0.05$).[37]

These benefits have not been seen consistently across all cohorts. In a retrospective study involving 287 pregnant women with PPROM between 23 and 33^{+6} weeks' gestation, DiGiulio et al.[34] concluded that extended 7-day azithromycin administration was associated with significantly increased latency (>3 days) compared to those treated with a 2-day routine azithromycin regimen. There were no effects on other maternal or neonatal outcomes. However, a systematic review and meta-analysis showed no difference in the risk of severe GM-IVH following antibiotic treatment for PPROM (RR: 0.73; 95% CI: 0.42–1.26; $I_2 = 0\%$, 4 RCTs, $n = 893$ participants; certainty of Evidence/CoE: low).[35]

Antenatal Corticosteroid Therapy

Antenatal steroids (ANS) such as dexamethasone or betamethasone can lower the risk of GM-IVH in preterm infants. These protective effects likely involve multiple mechanisms: accelerated maturation of the cerebral vasculature with improved vasomotor responses; decreased need for respiratory support/increasing surfactant

production and consequently improving lung compliance, stabilization of alveolar and capillary membranes that lowers permeability and the risk of inflammation, and promotes structural support through pericyte recruitment. Steroids also likely suppress inappropriate expression of vasoactive mediators such as angiopoietin and vascular endothelial growth factors and, consequently, prevent dysregulated angiogenesis and associated formation of unduly fragile and immature capillary networks in the GM and beyond.[38–40] In addition, steroids may also have indirect protective effects that involve suppression of systemic inflammatory responses, improvements in respiratory function with less need for mechanical ventilation, and the systemic acid-base balance, all of which can potentially alter cerebral blood flow.[41] McGoldrick et al.[39] reported a reduced risk of GM-IVH following ANS administration (RR: 0.58; 95% CI: 0.45–0.75; 8,475 infants; 12 RCTs, CoE: moderate; 1.4% fewer, 95% CI: 0.8–1.8% fewer). Korcek et al.[38] also reported a lower risk for any GM-IVH (OR: 0.58; 95% CI: 0.39–0.85; $p = 0.006$) and for high-grade GM-IVH (OR: 0.36; 95% CI: 0.2–0.65; $p < 0.001$) following a complete course of ANS.[38] However, many studies have shown variable results. Williams et al.[42] reviewed different steroid regimens for accelerating fetal lung maturation but found minimal or no difference in the risk of GM-IVH (RR: 0.71; 95% CI: 0.28–1.81; 4 RCTs, $n = 1,902$ participants; $I_2 = 62\%$, CoE: low). In another study, Walters et al.[43] reviewed repeated doses of prenatal steroids for women at risk of preterm births and reported with moderate certainty that the evidence for reduction in severe GM-IVH was equivocal (RR: 1.13, 95% CI: 0.69–1.86; 7 RCTs, $n = 5,066$ infants). Similarly, Blankenship et al.[44] detected no difference in the risk of GM-IVH in preterm, small for gestational age (SGA) infants who had received ANS (OR: 0.82; 95% CI: 0.56–1.2; 7 studies). Razak et al.[36] performed a meta-analysis of data from 9 RCTs ($n = 4368$ participants) and found a small reduction in the risk of severe GM-IVH risk with ANS (RR: 0.54; 95% CI: 0.35–0.82; $I_2 = 36\%$, aRD, –1% 95% CI, –2% to –0%); NNT 80 (95% CI: 48–232; CoE: moderate). However, there was no treatment effect for other interventions, including betamethasone vs dexamethasone for lung maturity (RR: 2.17; 95% CI: 0.89–5.25, $I_2 = 0\%$, 4 RCTs, $n = 1956$ participants, CoE: moderate), or repeated vs a single course of steroids (RR: 1.06; 95% CI: 0.73–1.56; $I_2 = 13\%$, 8 RCTs, $n = 5,472$ participants, CoE: moderate).

Magnesium Sulfate

Antenatal magnesium sulfate ($MgSO_4$) is a frequently used tocolytic medication that can temporarily stop or slow down uterine contractions to prevent preterm births. Antenatal $MgSO_4$ promotes myocardial stability in mothers, improves placental and fetal neural blood supply, reduces ischemic changes, and has antioxidant effects, especially in the brain, against apoptosis and hypoxia.[45,46] It also normalizes platelet aggregation.[47–49]

A subgroup analysis focusing on the $MgSO_4$ regimen showed that a single 4g dose of $MgSO_4$ can protect again GM-IVH (RR: 0.86, 95% CI: 0.66–1.12; $I_2 = 0\%$; $p = 0.473$).[50] Another subgroup analysis based on gestational age showed that the effect of $MgSO_4$ on GM-IVH in premature infants between 24 and 37 weeks and <34 weeks was 0.93 (95% CI: 0.83–1.05; $I_2 = 74.1\%$; $p = 0.009$) and 0.92 (95% CI: 0.7–1.18; $I_2 = 56.7\%$; $p = 0.099$), respectively.[50] The same investigators noted a significantly lower risk of severe GM-IVH (adjusted OR 0.248 (95% CI: 0.092–0.66, $p = 0.006$) in very preterm infants exposed to antenatal $MgSO_4$. Other groups have noted similar results.[49,51] However, the results have not been consistent across all studies. Razak et al.[36] did not find any effect of antenatal $MgSO_4$ on the risk of severe GM-IVH (RR: 0.8; 95% CI: 0.61–1.06; $I_2 = 10\%$; 6 RCTs, $n = 4,559$ participants; CoE: moderate). A recent meta-analysis of 7 pooled studies also did not show a significant protective effect of antenatal $MgSO_4$ on GM-IVH in preterm infants (RR: 0.8, 95% CI: 0.63–1.03; $I_2 = 63\%$; $p = 0.013$, $n = 7,236$ infants).[50]

Tocolytic Agents other than $MgSO_4$

There are various established guidelines for using tocolytic agents with mothers at high-risk for preterm labor. Most international guidelines, including those from The American College of Obstetricians and Gynecologists (ACOG), do not approve of long-term use of tocolytics because even though these medications may delay preterm births, the effects on neonatal outcomes are not consistently positive.[52,53] Some studies recorded adverse effects on infants. In a retrospective literature review on antenatal use of tocolytics and GM-IVH, Doni et al.[54] evaluated 241 very preterm infants who were exposed to antenatal indomethacin given as a tocolytic; multivariate analysis of the study showed a possible association between antenatal indomethacin and all degrees of GM-IVH (OR: 3.16; 95% CI: 1.41–7.05). Hammers et al.[55] systematically reviewed 27 observational studies with 8,454 infants (1,731: antenatal indomethacin exposure and 6,723: not exposed). The risk of severe GM-IVH (RR: 1.29; 95% CI: 1.08–1.71) and periventricular leukomalacia (RR: 1.59; 95% CI: 1.17–2.17) was higher in the antenatal indomethacin exposure group.

Pinto Cardoso et al.[56] assessed death and/or GM-IVH (primary outcome) in preterm infants between 24 and 31 weeks' gestation from the French 2011 EPIPAGE-2 cohort. Groups of preterm infants with vs without tocolytic exposure and groups with atosiban (oxytocin receptor antagonist) vs calcium channel blocker exposure were compared. Death and/or GM-IVH were not significantly different in preterm infants with vs without tocolytic exposure [183 of 363 (50.4%) vs 207 of 363 (57.0%); RR: 0.88; 95% CI: 0.77–1.01; $p = 0.07$]. The secondary outcome (death and/or grades III-IV IVH) was significantly lower in preterm infants with vs without tocolytic exposure [92 of 363 (25.3%) vs 118 of 363 (32.5%); RR: 0.78; 95% CI, 0.62–0.98; $p = 0.03$]. A secondary analysis of the APOSTEL-III trial, where 102 Dutch women were treated with nifedipine or atosiban for threatened preterm labor between 25 and 34 weeks' gestation, showed no differences in overall brain injury (abnormal cranial ultrasounds).[57] In another study, Weintraub et al.[58] reported a lower incidence of severe GM-IVH in preterm infants (24–32 weeks) exposed antenatal to ritodrine, a betamimetic tocolytic, compared to magnesium sulfate or indomethacin. Ritodrine has been removed from the American market due to adverse cardiovascular effects, but is occasionally still used as a tocolytic internationally.[59–61]

Delivery and Stabilization

Type of delivery: Korcek et al.[38] showed a borderline reduction in GM-IVH following a Cesarean section (CS; OR: 1.85; 95% CI: 0.98–3.51, $p = 0.057$). Other studies have also indicated that elective CS protects against GM-IVH in preterm infants, and perhaps antenatal steroids in combination with CS might have further enhanced this protection in extremely preterm infants born between 24 and 25 weeks gestation.[42,57,62–64] The ACOG suggested CS might be considered and recommended for preterm infants at a gestational age of 23–24 weeks and 25 weeks, respectively. Similarly, Karayel Eroglu et al.[65] reported lower rates of GM-IVH in preterm infants <34 weeks' gestation following CS. Humberg et al. from the

German Neonatal Network also showed elective CS reduces the risk of GM-IVH in infants <30 weeks' gestation.[66] Huang et al.[67] studied 826 Taiwanese infants and found a similar reduction in the risk of GM-IVH in CS-delivered infants between 22 and 25^{+6} weeks' gestation.

The benefits are not so clearly discernible at 2 years of corrected age. In two studies, Rahman et al.[68] and Ljustina et al.[69] did not detect a notable effect of CS on the incidence of GM-IVH in preterm infants born at the gestational age of 27–$34^{+0/7}$ weeks. Luca et al.[70] also did not find any association between the delivery mode and

Delayed cord clamping (DCC): Delayed cord clamping can be an important adjunct to the GM-IVH bundle.[32,71] The ACOG recommends DCC in all preterm neonates for at least 30–60 seconds.[72] A Cochrane review analysis reported that compared to early cord clamping (ECC), DCC decreases any GM-IVH with high-certainty evidence (RR: 0.83; 95% CI: 0.70–0.99); mortality with moderate-certainty evidence; and severe GM-IVH and periventricular leukomalacia (PVL) with low-certainty evidence.[73] Many other studies support a similar protective effect of DCC against GM-IVH in preterm neonates.[74–76] In utero, oxygenated blood from the placenta passes through the umbilical vein to the right atrium. However, pulmonary vasoconstriction can cause this blood to bypass the lungs and flow directly across the foramen ovale and the ductus arteriosus to the systemic circulation. After the onset of breathing, atmospheric oxygen is delivered to the pulmonary vascular bed, with consequent pulmonary vasodilation. It increases right ventricular output, leading to an upsurge in blood flow from the low-resistance placenta to the neonate.[77] Early cord clamping with immature respiratory drive can compromise left ventricular preload. There might be a two-edged effect: (A) a substantial amount of blood remains within the placenta after birth, and (B) pulmonary vasoconstriction and consequently restricted pulmonary blood flow further limits left ventricle filling. Early cord clamping is defined as clamping the umbilical cord <30 seconds after birth. There is a lower total blood volume and, thus, an increased likelihood of neonatal anemia and risk of intestinal injury, as well as GM-IVH.[78,79] Delayed cord clamping can benefit by reducing IVH. The delay in cord clamping has been traditionally defined as >30 seconds, but a longer duration of ≥60 seconds, until the cord pulsations fade, might be even more effective (level of evidence: 1a).[73,80,81] Delayed cord clamping adds about 5–20 mL/kg blood from the placenta into the newborn circulation, and consequently, lengthens the time for postnatal reduction in pulmonary vascular resistance.[82,83] Delayed cord clamping might be protective due to improved cerebral vascular autoregulation and fewer fluctuations in systemic perfusion.[83] In most studies, there is information on the placement of the infant's head vis-à-vis the mother's bed; the infant's head has been positioned with gravity to enhance flow to the infant. There are concerns that head elevation could adversely affect cerebral blood flow due to low umbilical venous pressures.[62] However, none of the trials have shown whether a combination with subsequent midline head positioning could have added benefits.[84]

A recent Cochrane review of 48 studies involving 5,721 babies and their mothers analyzed data from 40 studies involving 4,884 babies and their mothers. Infants born at 24–36^{+6} weeks› gestation and multiple births were included. Delayed cord clamping was seen to have slightly reduced the number of infants with any Grade IVH: Average risk ratio (aRR) (0.83, 95% CI: 0.7–0.99, 15 studies, 2,333 babies, high certainty) but not alter the number with severe IVH (grades III and IV) (aRR 0.94, 95% CI: 0.63–1.39, 10 studies, 2,058 babies, low certainty).[73] In most studies, the need to discontinue DCC originated from maternal/neonatal instability, fetal anomalies such as diaphragmatic hernia, disrupted placental circulation, monochorionic twins, intrauterine growth restriction, and hydrops fetalis.[78,85,86] A study of 474 infants in 2019 raised concerns about a high incidence of IVH associated with umbilical cord milking. It was stopped early when more IVHs were seen for preterm infants (23–27 weeks' gestation) than in similar infants in the DCC group.[62] Hence, cord milking is not recommended in preterm infants < 28 weeks' gestation. Globally, most centers lean towards trying DCC for infants born at ≥ 32 weeks' gestation.

Table 1: Main components of the "Golden Hour" strategy

1	Antenatal counseling, team briefing, and debriefing
2	Delayed cord clamping
3	Prevention of hypothermia (maintain temperature 36.5–37.5°C)
4	Timely and appropriate respiratory support
5	Cardiovascular system support
6	Nutritional support to prevent hypoglycemia
7	Infection control
8	Laboratory investigations to provide minimal handling afterwards
9	Monitoring and record keeping.
10	Family counseling

Golden-hour Management

Preterm infants are often ill-equipped for spontaneous transition to extrauterine life. Many require resuscitative help in the delivery room. There is sufficient evidence to support that preterm neonates should receive timely delivery room CPAP for better respiratory stabilization in the form of a decreased need for surfactant and mechanical ventilation.[87] However, this need for delivery room support can be an independent risk factor for GM-IVH in preterm neonates.[88] A retrospective study from Japan further showed that delivery room intubation was associated with an increased risk of severe GM-IVH.[89] The Golden Hour strategy is an evidence-based, standardized, structured care program supporting fetal-neonatal transition. This approach can be important for reducing the incidence of GM-IVH as nearly 50% of GM-IVH cases occur within the first 24 hours of birth, which can be altered with proper resuscitation in the delivery room and stabilization in the Neonatal Intensive Care Units.[90] Preventive measures should be implemented before this critical time frame. Golden Hour management has improved many short- and long-term adverse outcomes in extremely premature ELBW infants.[91–97] Short-term complications may include hypothermia, hypoglycemia, and respiratory and cardiovascular instability, which seem relatively benign but can increase the risk of GM-IVH. Most complications may be preventable with proper interventions during this crucial period. Indeed, there is some evidence that the Golden Hour strategy can significantly reduce the incidence of GM-IVH (level of evidence: 1a) (Table 1).[91,98]

Gentle Care

Transportation: There is a need for cautious transportation of at-risk premature infants to prevent GM-IVH. Outborn neonates, born in facilities without an appropriate-level NICU, experience logistical challenges during transfer to tertiary perinatal centers. Data show that preterm infants delivered in tertiary perinatal

centers have better outcomes, including fewer GM-IVHs, than those born in less-equipped hospitals and then transferred to tertiary centers for subsequent management.[99,100] These data were further supported in a large retrospective multicenter study of nearly 67,600 VLBW infants, where those who were transported within the first 48 hours after birth showed a higher frequency and severity of GM-IVHs.[101] Similarly, Towers et al.[102] showed a higher risk for significant GM-IVH (Grade III or IV) in VLBW infants born in level 1 nurseries and transported to higher centers than those born at their level 3 facility. Transport of preterm infants between facilities is believed to be an independent risk factor for GM-IVH and acute brain injury.[103,104] In one study, the incidence of GM-IVH was 27.4% in transported infants, compared to 13.42% in non-transported infants. The adjusted OR was 1.75 (95% CI: 1.64–1.86, $p < 0.001$).[100] The relationship between the transportation of VLBW newborns between hospitals and their susceptibility to GM-IVH is not completely understood and is possibly multifactorial. Vigorous manipulations, kinking or obstruction of the endotracheal tube, accidental extubation, or iatrogenic trauma while moving the infant. Exposure to low body temperature and unstable temperature during transportation can negatively affect blood flow to organs, leading to lactic acidosis, and possible delay in providing nutrition that may lead to hypoglycemia. This condition may be linked to GM-IVH; however, this correlation is not definitive.[100]

Hypothermia and temperature instability during transport could compromise organ perfusion and cause lactic acidosis, increasing the risk of GM-IVH.[102,105,106] The presence of transport hazards such as noise, vibration, acceleration and deceleration forces, additional handling, temperature fluctuations, and space and movement limitations, along with the need to address clinical deterioration, highlight the importance of creating, implementing, or strengthening a GM-IVH bundle in pre-transport management.[107]

Several steps can be useful components for preventing neurological injury in VLBW infants during transport in hospitals that handle the delivery before the transportation of VLBW newborns and in hospitals that offer interhospital transport for additional care. If there are no maternal risks or imminent delivery, *in-utero* transport to a hospital with an appropriate tertiary care NICU improves the overall outcomes in preterm neonates.[108] Similarly, telemedicine effectively expands access to quaternary neonatal care for rural communities and level I and level II NICUs, reduces potentially-avoidable transfers of newborns to level III and IV NICUs, helps in the triage of neonatal transfers, promotes family-centered care and reduces healthcare costs.[109,110]

Implementation of a prevention bundle for hypothermia has been shown to reduce the incidence of GM-IVH.[111] Placing polyethylene bags before cord clamping as an isolated intervention has not changed the proportion of neonates with normothermia.[112,113] Existing data show that maintaining normothermia (36.5–37.5°C) during and after the golden hour in all neonates born <34 weeks' gestation can help prevent hypoxic-ischemic encephalopathy (HIE). Using snap-open access port covers or air-boosts on transport incubators reduces hypothermia.[114] Use of gel-filled thermostable mattresses, cots with water-filled mattresses, maintaining delivery room temperatures at >25°C, reducing maternal hypothermia before delivery, providing plastic bags/wraps, and caps for the newly born infants, using warm resuscitation gases, room humidity optimized for the country, season, and gestation may decrease hypothermia at NICU admission and be associated with a lower risk of severe brain injury and mortality.[115–123] Double-walled whole-body polyethylene bags, either as an isolated step or in combination with an exothermic mattress, can increase the risk of hyperthermia and preterm brain injury.[124–128] Surface temperature (axillary) may be sensitive to hypothermia but not hyperthermia.[113] Non-invasive temperature measurements using non-contact infrared thermometers (NCITs) and infrared thermographic (IRT) have shown a reasonable accuracy of ± 0.3°C in various settings but have not been evaluated during transport. The performance of these devices has been influenced by measurement location, the type of sensor, the reference and tool, individual physiological attributes, and the surrounding environmental conditions.[129]

Noise and vibration could be important variables in the causation of GM-IVH, particularly during transfer. The cerebral vasculature in premature infants is still not fully developed in structure and has also not matured with autoregulation. Indeed, noise and vibration have been associated with fluctuations in blood pressure, heart rate, and respiratory rates, leading to variability in cerebral blood flow and consequent risk of GM-IVH.[130–133] The American academy of pediatrics has (AAP) recommended that sound levels in the NICU should not exceed 45 dB. The International Electrotechnical Commission (IEC) recommends standard maximum sound levels of <60 dBA for transport incubators and vibration levels of < 0.31 m/s^2.[24,134] Having GM-IVH bundles with ongoing staff education programs and staff awareness of monitoring noise and sound levels that reach the neonate during transport can diminish the effects of stress on the babies' cardiovascular, respiratory, neurological, and endocrine systems and reduce adverse neonatal outcomes. The current sound levels in the transport incubator range from 47 to 55 dB. In an observational study, peak sound levels ranged from 80.4 to 86.4 dBA in rotor wing air transport (RWAT) with whole-body vibrations (WBV) of 1.68–5.09m/s^2. In ground ambulance transport (GAT), the noise was 70.3–71.6 dBA and WBV 1.82–3.96m/s^2.[111] Silicone ear plugs or earmuffs can reduce sound level exposure, and gel mattresses can lower the vibration in air transport. These benefits from vibrations were not evident in GAT.[135] Early encouraging data suggest that non-contact active noise cancellation (ANC) devices deserve further testing.[136] Dedicated Neonatal transport service and newborn emergency transport service (NETS) teams can reduce transport-related morbidity and mortality.[137,138] These teams can be comprised of registered nurses, respiratory therapists, physicians, and paramedical staff.[139] They can help stabilize the infant prior to transfer, including with delivery room resuscitation at the peripheral centers.[140] Thus, although inter-hospital transport increases the risk of GM-IVH, careful training and preparation, including experienced personnel, and strict adherence to guidelines can help. The goal is to ensure these vulnerable newborns receive the highest standard of care while minimizing potential harm and improving their outcomes.

Neonatal Intensive Care Unit (NICU) Management

Nursing Care

Head positioning: Optimizing care practices to ensure adequacy and less variability in the cerebral blood flow of preterm infants is crucial in the first 72 hours after delivery. Maintaining a neutral head position and minimizing head tilt could prevent jugular venous obstruction and subsequent ipsilateral venous congestion.[141,142] Early in the literature review, from 1980 to 2010, 10 articles were clinical trials, providing either type III evidence using a quasi-experimental, non-randomized convenience sample design or, in expert opinion, reporting an increased cerebral blood volume or

decreased jugular venous flow with head position/tilting. These explain the changes in cerebral oxygenation (increased cerebral blood velocity and/or increased intracranial pressure), with the head position as likely to be secondary to the occlusion of the jugular venous drainage, which could increase the risk of GM-IVH in premature infants (low certainty of evidence). Another observational discussion by the investigators was the connection between head tilting and brain hemodynamics. They concluded that an increased cerebral blood volume and/or intracranial pressure may result from the infants' potential inability to autoregulate cerebral blood flow adequately.[143]

A Cochrane review in September 2019 identified 3 RCTs with a total of 290 infants (either < 30 weeks' gestational age or < 1000 gm body weight) on the effects of head midline position on GM-IVH in very preterm infants. Two of them compared the midline position to the head rotated at 90° with the flat cot. The third trial compared the supine midline head position with the head rotated 90° and the bed tilted at 30°. The result of this trial did not show any effect on rates of GM-IVH with RR: 1.11, 95% CI: 0.78–1.56, and severe GM-IVH with RR: 0.71, 95% CI: 0.37–1.33. Neonatal mortality (RR: 0.49, 95% CI: 0.25–0.93) was lower in the supine midline head position.[144] However, the certainty of the evidence was very low for all outcomes, primarily due to the limitations of the study design. High-quality RCTs are needed to resolve this uncertainty. Studies have also shown that when we support infants in a tucked flexed position, with hands to the midline or near their face, we enhance autonomic stability and promote relaxation, which, in turn, can be beneficial for premature infants by promoting self-regulation, maximizing stability, optimal breathing patterns, reserving energy, and fostering overall growth and development.[143,145] After benchmarking NICU centers with low GM-IVH rates were reported to the Vermont Oxford Network and reviewed, the experts identified midline positioning aligned with the torso and 30º bed elevation as potential best practices, but without proven evidence. This practice is essential to avoid fluctuations in intracranial pressure that may increase the risk of acute brain injury.[142]

Handling care: Nurses play a critical role in interventions in the first 72 hours of life, a period when preterm infants are most susceptible to GM-IVH.[146,147] As stated earlier, the nurse should maintain the infant in a comfortable, midline, flexed, and contained position with the infant's limbs flexed and tucked using appropriate positioning aids and boundaries.[147,148] Maintaining the hands near the face and gently repositioning the baby after extending their limbs during exams and procedures is another IVH prevention nursing measure.[149] For handling preterm and sick babies, the nurses should gently handle the babies with slow, controlled movements. They should act as a team and seek assistance from additional nurses for procedures or complex handling maneuvers.[141,143] All these recommendations are based on potential best practices. It has been advised to avoid routine suctioning for preterm newborns unless there are objective reasons to warrant it.[150]

Blood withdrawal: Another nursing element that warrants careful attention is avoiding rapid blood withdrawal of blood from the umbilical arterial line. This practice is associated with a transient but significant drop in cerebral blood flow. Previous studies have noted low cerebral tissue oxygen saturations ($CrSO_2$s) and increased $CrSO_2$ variability in real-time NIRS monitoring during umbilical arterial blood sampling. The assumption here is that temporary changes in cerebral blood flow led to increased cerebral tissue oxygen extraction. Whether patient or procedure-related factors are the primary contributors to this phenomenon remains unclear.[64,151]

The impact of the sleep-wake cycle on the risk of IVH is plausible yet unproven. Sleep is crucial to brain development, especially for 22–36 weeks-old gestation premature infants.[152] Sleep patterns begin to mature around 28 weeks' gestation, with most of the sleep time being in REM sleep.[153] The percentage of REM decreases with development. This critical period allows adequate neuronal maturation, ranging from neuronal differentiation, migration, and myelination to synapse formation and elimination to central visual development and relationships with the other sensory systems.[154] Recent literature suggests better practices for preserving and promoting infant sleep within the NICU.[152] It is well recognized that the sleep-wake cycle directly impacts brain development and future learning and is associated with improved long-term developmental outcomes.[152] While term infants sleep around 70% of the day, expected preemies sleep even more. However, more studies are required to determine the exact sleep requirement for developing the preterm brain. In 2005, Holditch-Davis et al. assessed sleep-wake states in 71 preterm infants. Evaluation occurred over 3 years, with 51 enrolled looking at IQ, motor development, and the home environment. The preterm infants that developed REM sleep more rapidly showed the best outcomes (Mean et al. scores, language development, and fine motor skills).[155] Based on available data, assessing the infant's sleep-wake cycle is essential to evaluating the appropriate timing for positioning and caring. Minimizing disruptions, repositioning the infant gently and carefully at fixed intervals, and aligning care activities with the infant's sleep-wake states whenever possible played a positive role.[64]

To reduce the stress on critically-ill infants, the nurses should use minimal handling techniques and suction the infants very gently and infrequently.[150] Routine endotracheal suction should be avoided. These protocols reduce stress and hemodynamic fluctuations. This nursing care, again, is based on best practices (level of evidence: 5).

Respiratory Management

Surfactant therapy could reduce the risk of GM-IVH. The relation between the use of surfactants and improved preterm survival has been well established.[156] Until recently, one protocol for surfactant delivery involved Intubation, Surfactant delivery, and Extubation (InSurE) followed by support with a continuous positive airway pressure device. However, in view of the requirement of intubation and bag and mask ventilation in this technique, alternative, less invasive approaches have been evaluated. Surfactant instillation via a laryngeal mask, aerosolization, and thinner catheters have all been evaluated. Using a thin or more flexible catheter for surfactant delivery appears to have been associated with enhancing neonatal outcomes, including a decrease in the need for mechanical ventilation in the first 72 hours.[157] A recent Cochrane review of 16 studies and 2,164 neonates concluded that less invasive surfactant administration (LISA) with surfactant administration with ETT significantly reduced the need for intubation within 72 hours (RR: 0.63, 95% CI: 0.54–0.74), risk of the composite outcome of death or BPD at 36 weeks' postmenstrual age (RR: 0.59, 95% CI: 0.48–0.73), severe GM-IVH (RR: 0.63, 95% CI: 0.42–0.96), death during first hospitalization (RR: 0.63, 95% CI: 0.47–0.84), and BPD among survivors (RR: 0.57, 95% CI: 0.45–0.74).[158] Techniques such as surfactant administration through the laryngeal or supraglottic airway (SALSA) and aerosolized surfactants are

currently being investigated.[159] Surfactant therapy and mechanical ventilation have reduced the mortality related to RDS, but there could have been increased rates of GM-IVH. Further studies are needed to explore these associations.[160] Increasing data suggest that non-invasive respiratory support can improve outcomes over intubation and mechanical ventilation, even though some infants will need lifesaving assisted ventilation at birth or during a NICU stay.[161,162] The risk of intubation and mechanical ventilation increases with decreasing gestation, as does the risk of GM-IVH. A recent Cochrane review of 20 RCTs showed that volume guarantee ventilation lowered the risk of Grade 3 or 4 GM-IVH compared to pressure-limited mode.[163]

The effects of high-frequency oscillatory ventilation (HFOV) on GM-IVH and other neurological outcomes remain controversial and inconclusive. Some RCTs have shown that HFOV could increase the risk of all grades of GM-IVH, but the results were not consistent.[164,165] At 2 years of age, the outcomes did not clearly differ between the two groups.[166] There is a need for further study with appropriately sized samples.

Oxygenation: Current evidence suggests using blenders in the delivery room with FiO_2 of 30% for <28 weeks and 21–30% for those born between 28 and 31 weeks.[167,168] In addition to promptly starting SpO_2 monitoring after birth, the recommendation is to modulate FiO_2 to achieve SpO_2 >80% by 5 minutes after birth, since there is a demonstrated association between hypoxia at this time point and increased mortality and GM-IVH.[169] The immature GM is very fragile and prone to hyperoxia-induced free oxygen radical injury as well as hypoxia. For this reason, several RCTs and meta-analyses have been conducted to define "the perfect" oxygen saturation in neonates.[170,171] To balance the risks of retinopathy vs injury to other organs, oxygen concentrations may need careful titration based on gestation and birth weight.

Permissive hypercapnia: A key goal of respiratory assistance is to achieve adequate ventilation (CO_2 elimination). Hypocapnia ($PaCO_2$ <35 mm Hg) is associated with cerebral vasoconstriction and associated white matter injury, whereas hypercapnia is linked to increased cerebral blood flow with a subsequent increased risk of GM-IVH.[172] Though experimental studies showed a beneficial effect of higher $PaCO_2$ on the lung, studies in ventilated preterm neonates showed no clinical benefits.[173] Currently, there are no safe thresholds to define permissive hypercapnia. Severe hypercapnia is associated with an increased risk of GM-IVH. Apart from this, fluctuations in $PaCO_2$ levels have been found to have a more deleterious effect on the severity of GM-IVH.[174] Avoiding $PaCO_2$ levels of >60 mm Hg during the first 72 hours of life in preterm neonates is recommended.[175] Assisted ventilation should be provided to optimize gas exchange while minimizing lung injury and its associated morbidities.[174]

Hemodynamic Management

Treating hypotension: There is no consistent definition of hypotension or a standardized approach to its management in preterm infants.[148] Blood pressure levels <5th percentile for gestational and postnatal age are considered concerning.[176] Lightburn et al.[148] found no significant difference in cerebral blood flow velocities between ELBW infants with and without documented hypotension. However, other studies have linked the use of vasopressors for treating hypotension in preterm infants to an increased risk of developing GM-IVH and other brain injuries.[177,178]

A Cochrane review of 8 RCTs did not find evidence to support the routine use of volume expansion in preterm infants without cardiovascular issues or in infants with cardiovascular compromise when outcomes such as severe disability, cerebral palsy, or mortality were reviewed.[179] A cautious approach is recommended; a slowly infused fluid bolus may be useful before initiating inotropes. Inotropes should be considered when low blood pressure is associated with a prolonged capillary refill, decreased urine output, elevated lactate, or abnormal echocardiography findings (grade B recommendation).[180]

Management of a patent ductus arteriosus (PDA): Patent ductus arteriosus is a common morbidity of the preterm infants. The presence between PDA has been linked to various morbidities in neonates, including intraventricular hemorrhage.[181,182] The association of PDA and GM-IVH is complex. Although many studies suggest that the presence of hemodynamically significant PDA has been associated with GM-IVH.[183,184] Many other studies have contradictory results that negate its considerable direct effect on cerebral circulation.[180,185] Patent ductus arteriosus and its relation to GM-IVH is a complex interplay of various factors between the susceptible host, hypoperfusion, hemodynamic changes by PDA, coagulation, and subsequent exposure to reperfusion and pharmacological agents used to treat PDA.

Hemodynamic changes due to PDA: Cerebrovascular autoregulation plays an important role in maintaining adequate cerebral perfusion. Numerous studies have demonstrated that premature infants have impaired cerebrovascular autoregulation.[186,187] The association of hemodynamically significant PDA with GM-IVH needs further study. Significant PDA in the presence of cardiac immaturity and increased cerebrovascular reactivity could contribute to GM-IVH. Significant controversy prevails around the management of PDA, and several care pathways are being followed, including conservative management, aggressive treatment, targeted treatment, or surgical ligation. The outcomes need to be carefully studied.

Conservative approach in PDA management: This is a highly-debated approach to managing a hemodynamically significant PDA. Sung et al.[188] compared two epochs. Epoch I (July 2009–Dec 2011) and Epoch II (Jan 2012–Jan 2014) in the management of PDA in ELBW infants, comparing a nonintervention approach vs a mandatory closure approach in infants with a PDA >2 mm. In Epoch I, PDA was managed with indomethacin followed by surgical ligation, and nonintervention was used in Epoch II. There were no significant differences in mortality or morbidities like necrotizing enterocolitis or intracranial hemorrhage (ICH). Interestingly, in Epoch II, despite longer exposure to PDA, rates of BPD were lower. During the same period, another study in the US that included over 5,000 VLBW infants showed contradictory findings suggesting that while the rate of PDA intervention decreased, there was an increase in morbidities like bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and acute renal failure.[189] Hence, extrapolating these findings to various populations and centers is difficult and requires further investigation.

Prophylactic closure: Early prophylactic indomethacin, if it started earlier, between 6 and 12 hours of life, and continued every 24 hours for a total of 3 doses, has been shown to decrease the incidence of any GM-IVH (RR: 0.88, 95% CI: 0.8–0.98), and severe GM-IVH (RR: 0.66, 95% CI: 0.53–0.82) in extremely low birth weight neonates.

It decreased the incidence of hemodynamically significant PDA and the need for surgical ligation. Still, it did not change motor/sensory outcomes at 36 months of corrected age.[190,191] However, a large case-control study of 633 infants showed a higher risk of spontaneous bowel perforation when babies were exposed to indomethacin during the first three days after birth compared with control infants [odds ratio (OR) 1.86, $p < 0.0001$].[192] Also, a retrospective analysis of the ELBW cohort in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network showed similar results when it was used for PDA closure with a therapeutic, not prophylactic intent (adjusted OR: 1.61, 95% CI: 1.25–2.08, $p < 0.05$).[193] However, no randomized control trials comparing prophylactic indomethacin to placebo (including a Cochrane meta-analysis) have shown an increased risk of SIP or NEC.[194] The incidence of severe GM-IVH was dramatically decreased in infants born at <29 weeks who had not received any antenatal steroids.[195] There could be a possible therapeutic window to treat <29 weeks' gestation premature infants with indomethacin who had received no or only partial antenatal steroids and had no sonographic evidence of GM-IVH.[196] On the other hand, prophylactic ibuprofen treatment did not show any reduction in GM-IVH. A 2011 Cochrane review indicated that ibuprofen prophylactic treatment did not significantly reduce GM-IVH (all grades or severity).[197] There is not much evidence on prophylactic acetaminophen and its effect on GM-IVH. Two randomized controlled trials with 80 infants indicate no appreciable improvement in patient-important clinical outcomes.[198]

Pain Management and GM-IVH

Newborns can detect, process, and respond to painful stimuli. Preterm infants may not only be more sensitive to pain due to immature inhibitory mechanisms, but they might also be exposed more frequently to painful procedures such as heel sticks/venipuncture for blood sampling.[199] In a large prospective multicenter trial in level III NICUs in Paris, neonates experienced an average of 115 (range, 4–613) procedures during the 6-week study period, with an average of 16 (range, 0–62) procedures per day of hospitalization.[200] There was clear evidence that pain and stress affect brain development adversely.[201] In rat pups, repetitive exposure to painful stimuli accentuated neuronal excitation and apoptosis in several cortical and subcortical areas, suggesting that pain and pain-related effects may have a widespread impact on the developing brain.[181] Pain-related stress during the early neonatal period can be associated with reduced white matter and subcortical grey matter maturation. Consistent findings can be noted in magnetic resonance (MR) imaging, 3D MR spectroscopic imaging (MRSI), and diffusion tensor imaging (DTI).[202] Many centers are now using near infrared spectroscopy (NIRS) to measure cerebral blood flow and oxygenation in the brain. There are clear differences in the NIRS signatures of pain-induced prefrontal activity vs. those induced by various emotional and stress responses used.[202] It is still unclear whether there is a direct causal relationship between pain and GM-IVH, but there is clear evidence that pain leads to stress-related neurodevelopmental changes. Therefore, pain-control measures should preferably be included in GM-IVH bundles.

Skin-to-skin contact, commonly known as "Kangaroo mother care" (KMC), is vital in providing comfort to neonates when allowed and is one of the primary methods of non-pharmacologic intervention for pain management.[203] Several studies are currently investigating the impact of KMC on the occurrence of GM-IVH. For KMC, infants are placed in a prone position on the parents' bare chest, enabling direct contact between the neonate and the parent.[204] Various research studies have shown the positive effects of KMC on easing the discomfort of neonates and significantly improving their overall outcomes. Kangaroo mother care strengthens mother-infant sensory interaction and induces hormonal and epigenetic processes to enhance preterm infant health.[29] It also mitigates pain, promotes bonding with parents, and increases breast milk supply. A study reported decreased mortality and improved long-term developmental outcomes with KMC. The relationship between KMC and GM-IVH is being investigated with interest. The British Association of Perinatal Medicine and Neonatal Society has implemented "side-lying KMC while maintaining midline position" to improve overall outcomes, including GM-IVH and pain control.[205] Collados-Gómez et al.[206] are conducting a trial to evaluate side-lying positions for hemodynamically stable <28 weeks' gestation neonates for various outcomes, including GM-IVH.[206] Although there is still limited evidence of utilizing KMC in premature neonates to reduce GM-IVH and improve pain control, studies are already showing the positive effects of KMC in easing the discomfort of neonates.[206] Similarly, early results suggest that swaddling to simulate the *in-utero* position in neonates might also enhance the level of comfort.[207] In neonates receiving some oral feeds, oral sucrose gel is another non-pharmacological intervention that has proven beneficial. It is a simple yet very effective measure for frequently-performed procedures such as heel sticks or venipunctures.[187] In short, KMC, swaddling, and oral sucrose are robust non-pharmacological interventions that enhance neonatal care for premature neonates and promote healthy neurodevelopmental care.

Noise Reduction and Controlled Environment

Many units have formed task forces/champions to alleviate noise by maintaining noise levels under 65–70 decibels (dB). In conjunction with maintaining noise level under 65 dB, placing noise reduction posters across the unit, rounding on patients away from their isolette, and adjusting the overall announcement and paging system to a lower decibel level have made it successful in maintaining NICUs to minimal stimulation units. Although there might not be a demonstrated direct relationship with IVH, low noise levels seem to be neuroprotective.[208]

Neonatal Thrombocytopenia and Platelet transfusion: A Complex Interplay

Neonatal thrombocytopenia: Studies have been reported that fetal/neonatal thrombocytopenia can increase the risk of IVH.[209] In a prospective study conducted by Kahn et al.[210] on VLBW infants, they reported that IVH Grade >2 was noted in 20.7% of infants with platelet counts <100,000/μL, which was significantly higher than 6.4% of those without thrombocytopenia. Some other studies have also shown that the risk of GM-IVH increases with the severity of thrombocytopenia.[211,212]

The association between thrombocytopenia and GM-IVH has not been consistent across all studies of critically-ill premature infants. Bolat et al.[190] focused on neonates in the NICU with thrombocyte counts $<50 \times 10^9$/L and found a higher prevalence of IVH ≥ Grade II in infants with thrombocytopenia (7.2%) than in those without thrombocytopenia (4.4%). However, these findings

were not significantly related to the level of the lowest platelet count. In a retrospective multicenter cohort study, Sparger et al. observed thrombocytopenia as a risk factor for IVH, but the severity of thrombocytopenia was not correlated with GM-IVH.[213] Von Lindern et al.[214] found that GM-IVH Grade ≥ II was higher in neonates with thrombocytopenia. However, after conducting a multivariate linear regression analysis, the risk in the subgroups of thrombocytopenic infants was not significantly different ($p = 0.3$). A recent systematic review of 6 studies summarized insufficient evidence for a causal relationship between platelet counts and the risk of GM-IVH in neonates.[215] The authors inferred that further study is needed to explore the possibility of confounding variables such as lower gestational age, intensity of illness, low birth weight, or sepsis. In some studies, IVH was discovered before the onset of thrombocytopenia, implying that the low platelet counts might not have been the direct cause.[214]

The importance of thrombocytopenia as a causative variable in GM-IVH is evident in studies of fetal/neonatal alloimmune thrombocytopenia (FNAIT). In this condition, there are fewer confounding factors. An observational cohort study of ICH caused by FNAIT from the International No IntraCranial Hemorrhage (NOICH) registry during the period 2001–2010 (13 tertiary referral centers from 9 countries across the world) examined 592 cases of FNAIT in the registry, and 43 confirmed cases of ICH due to FNAIT were noted. Most hemorrhages (23/43, 54%) occurred before 28 weeks' gestation.[216] Intracranial hemorrhage due to FNAIT is reported to occur in 1:12,500–25,000 births; it has been recorded more frequently at full-term birth as isolated ICH or its consequent clinical features, such as seizures, might not be noticeable in utero.[216] Fetal/neonatal alloimmune thrombocytopenia is caused by maternal alloantibodies directed against fetal platelets due to their incompatibility with human platelet antigens (HPAs).[217] Human platelet antigens -1a is a frequently incriminated antigen; the presence of HLA-DRB3*01:01 and HLA-DRB4*01:01P (*01:01 or *01:03) are important predictors of this isoimmunization.[218] Besides HPA-1a, HPA-5b is another possible antigen that may lead to FNAIT.[217]

Radder et al.[219] described 62 pregnancies among 27 mothers. They looked for the risk of ICH in successive pregnancies with thrombocytopenia, with or without a history of ICH. In 52% of the ICH cases, a previous sibling suffered from ICH. The recurrence rate of ICH in the subsequent offspring of women with a history of FNAIT with ICH was 72% (95% CI: 46–98%). Delbos et al.[220] showed that FNAIT-related ICH was associated with death in 59% of cases. In another study in the FNAIT registry, 389 people were studied; they were from Australia ($n = 74$), Norway ($n = 56$), Slovenia ($n = 19$), Spain ($n = 55$), Sweden ($n = 31$), the Netherlands ($n = 138$), and the USA ($n = 16$).[221] The median follow-up was 5 days (interquartile range, IQR 2–9). Severe thrombocytopenia (platelet count $<50 \times 10^9$/L) was reported in 283 (74%), and extreme thrombocytopenia ($<10 \times 10^9$/L) was reported in 92 (24%) neonates. Severe ICH was noted in 22 neonates.

Coagulation mediators: In addition to thrombocytopenia, we need further examination of coagulation mediators such as vitamin K reductase complex, apolipoprotein E (APOE)2, APOE4, endothelial nitric oxide synthase (eNOS *894G > T* and *–786T > C*), fibronectin 1, factor V Leiden mutation (Arg506Gln), and collagen 4A1 gene; these may play a role in GM-IVH development.[222–228] These mutations have also been implicated in cerebral hemorrhages.

Platelet transfusion threshold: The thresholds for platelet transfusions in neonatal thrombocytopenia have increasingly become more restrictive.[229–231] Andrew et al.[230] performed an RCT on thrombocytopenic ($50–150 \times 10^9$/L) preterm infants and found no difference in the incidence of bleeding between groups with and without platelet transfusion; this indicates that liberal PT might be unnecessary. In another retrospective study comparing liberal and restricted PT approaches in premature infants, no significant difference in hemorrhagic events was found between the groups.[214] Moreover, The PlaNeT-2 trial concluded that administering platelet transfusion at a lower threshold (below 25×10^9/L) resulted in lower mortality rates and fewer hemorrhage episodes than a higher threshold (PC below 50×10^9/L).[229] Several studies have shown fewer adverse effects in restrictive groups who received less platelet transfusion.[232] Kumar et al.[233] and Kasap et al.[234] also found that mortality and the GM-IVH rates were higher in the liberal transfusion group. There is a possibility that these findings might relate to the infants' clinical conditions or the properties of the transfused platelets, as those were obtained from adult donors whose platelets are hyperreactive and pro-inflammatory compared to those from infants. The actual protective value of platelets in the recipient thrombocytopenic neonates (placental counts $<20 \times 10^9$/L) is unknown. Based on current evidence, Curley et al.[229] and Kumar et al.[233] recommend relatively restrictive platelet transfusion thresholds. Since platelet transfusions can cause/augment systemic inflammatory responses, further studies are needed to determine safe, lowest-possible thresholds for platelet transfusions.[94,235]

Staff Education and Training

Continuing education in NICUs for providers and nursing staff can help promote the best, evidence-based practices to mitigate factors contributing to GM-IVH.[236] Application of strategies such as midline positing, Gentle handling, cluster care, and pain management soon after delivery could possibly help reduce GM-IVH.[237] Intermittent simulation training can also complement these ongoing education efforts.[237,238] These efforts can enhance the confidence and skills of the team, ultimately improving the quality of neonatal care and reducing the incidence of GM-IVH.[237] Frequently updated physician and nursing care guidelines can also be helpful.[152]

Other Neuroprotection Measures

Neurorestorative therapies: Multipotential stem cells, immunomodulation, and anti-inflammatory therapies have the potential to stall the progression of injury or improve neurodevelopmental outcomes.[239] Mesenchymal stem cells have been tried via intravenous and intraventricular routes, and both are safe. Prophylactic recombinant human erythropoietin therapy in very preterm infants improved cognitive outcomes at 18–24 months, without any effect on any other neurodevelopmental outcomes.[240] Low-dose melatonin (N-acetyl-5-methoxytryptamine) has benefited preterm sheep models.[241] Caffeine citrate (methylxanthine), azithromycin, and anakinra (Interleukin-1 receptor antagonist) are the other anti-inflammatory agents being studied to improve preterm brain injury.[242] Preterm neonates have high rates of clinical and subclinical seizures.[243] Magnesium sulfate infusions could help treat neurological injuries.[244] Similarly, haptoglobin levels are upregulated in the brain by oligodendrocytes after GM-IVH, and they act as scavengers of free hemoglobin and prevent free

hemoglobin-mediated cytotoxic injury.[245,246] Experimental animal studies have shown that haptoglobin infusion into the ventricular cavity may help control the adverse effects of GM-IVH.[246] However, many of the routinely used anticonvulsants have varying levels of neurotoxicity.[242]

Future Direction: Applying near-infrared spectroscopy (NIRS)

Near-infrared spectroscopy is a non-invasive tissue oxygenation and blood flow monitoring technology. It may have a potential preventable role in the incidence of GM-IVH in preterm infants. The principle of NIRS is to assess local changes in oxygenated and deoxygenated hemoglobin concentration in a body tissue region using near-infrared light (700–900 nm).[247] These two measures give a regional oxygen saturation reading for about 30% of the arterial and 70% of the venous components.[248] Near-infrared spectroscopy on the forehead calculates the $CrSO_2$ measurement.[249] The technology is based on the relative transparency of skin, bone, and connective tissue to near-infrared light, permitting estimation of cerebrovascular oxygenation and perfusion to a depth of 2–3 cm directly beneath the probe.[250,251]

Application of NIRS in GM-IVH prevention: Early detection of $CrSO_2$ provides real-time, continuous, and tissue-specific measures of oxygen saturation and tissue perfusion, enhancing current approaches to brain monitoring.[251] Cerebral regional oxygen saturation monitoring has provided evidence of a biphasic injury pattern, with an early rise in $CrSO_2$ due to hyperperfusion and a later drop due to tissue hypoxia.[250,252–254] Near-infrared spectroscopy may enable earlier recognition of the onset of cerebral hemodynamic changes, which is a crucial part of the pathogenesis of GM-IVH.[255] Real-time data can help clinicians know the right time to step in to prevent/diminish the likelihood of GM-IVH.[256] In one study, $CrSO_2$ trends in extremely preterm infants with GM-IVH during the first 72 hours of life were different from those of those without GM-IVH.[253] Another study showed that preterm infants with any grade of GM-IVH showed lower $CrSO_2$ for up to 4 weeks than non-IVH infants.[257]

Interventions guided by NIRS: Interventions that can be done based on NIRS, such as changing the ventilation parameters or implementing neuroprotective strategies, have promising results in preventing GM-IVH in preterm infants.[256] A recent report suggested that early detection of the fluctuations in $CrSO_2$ using a machine-learning model may help in the early initiation of therapeutic measures.[258] In normal infants, $CrSO_2$ values may vary depending on their gestational and chronological age and clinical condition.[259] Serial tracks may be more helpful than point measurements.[260] Near-infrared spectroscopy may be more useful with other monitoring systems for assessing cerebrovascular autoregulatory functions.[261,262] It should be viewed as an adjunct tool for monitoring.[250]

Challenges and Future Directions

Data interpretation and standardized monitoring protocols are the main challenges of implementing NIRS in neonatal care.[250] Standardized guidelines should be integrated into clinical practice. Further research is needed to assess the efficacy and cost-effectiveness of implementing NIRS-guided strategies to reduce GM-IVH.[263]

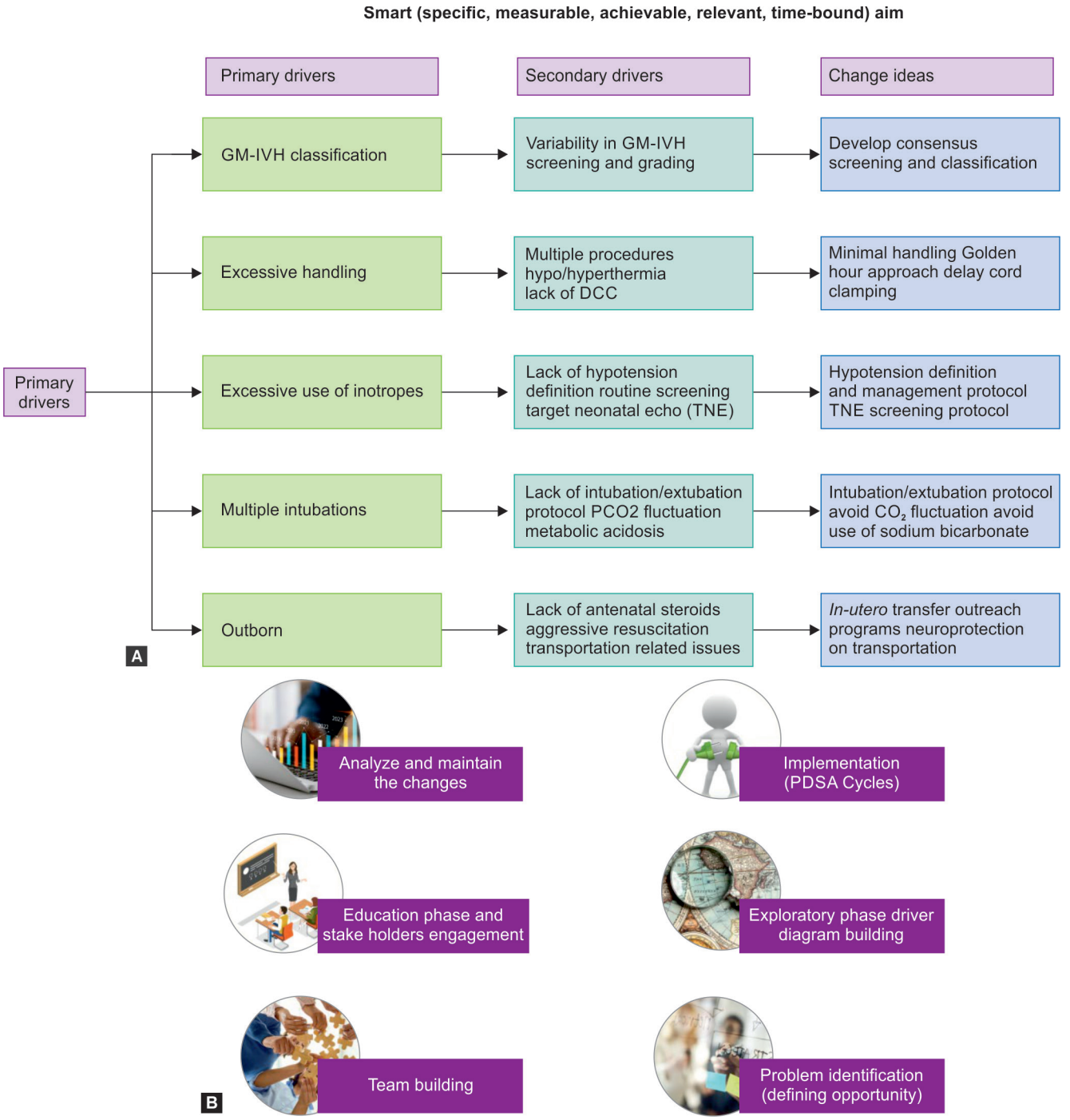
Technological advancement: Newer developments in NIRS technology, like broadband optical spectroscopy, have the potential to offer further information besides regional tissue oxygenation.[264,265] Such innovation could augment NIRS in preventing GM-IVH and other neonatal morbidities.[266] In conclusion, NIRS provides continuous information on cerebral oxygenation and blood flow and thus can direct targeted interventions to decrease the extent and prevent the occurrence of GM-IVH.[267] Considering the apparent safety of these non-invasive measurements, there is a high likelihood of widespread acceptance in routine, continuous measurements of cerebral hemodynamics.[250] Further research and clinical trials are needed to determine the full potential of NIRS in preventing GM-IVH and optimizing neonatal care.

Implementation Science

The bundle approach can effectively improve clinical outcomes in NICUs when researchers with evidence implement it into practice.[268] A dedicated leader is key to implementing a successful, potentially better practice. It is also vital to identify the areas for improvement within the unit, foster a sense of shared purpose, and collectively put it into action. When team members become aware of the issue and the QI initiative, they elaborate effectively to develop solutions and drive a positive drive to change. This effort is crucial for progress, leading to better outcomes: "The potential for positive change is immense and within our reach." Another important concept is optimal timing and sequence for implementing these bundles in NICUs, focusing on strategies of recommendation to improve the standardization of care bundles across multiple NICUs, with an eventual goal of consistency and reduction in variation. However, a high level of compliance is essential. Several ways have been described in the literature to improve the compliance of each care bundle. Once the area of improvement is determined and the primary target is set, a protocol will be developed based on evidence, followed by educational sessions for healthcare workers and providers. A systematic review of 47 studies conducted by Borgert et al.[269] showed that developing protocols, education materials, reminders, audits, and feedback are important strategies for implementing successful care bundles (Fig. 2).

Conclusion

The critical window period for brain injury is the first 72 hours of life, when 90% of premature infants are at risk of intraventricular hemorrhage. Most occur during the first 24 hours of life.[195] Based on assessed risk (Fig. 3), various interventions have been tried to decrease poor neurological outcomes during the pre-conceptional period (pre-implantation genetic diagnosis, folic acid supplementation), embryogenesis (avoidance of teratogenic drugs during critical stages of neural development), fetal period (treatment of chorioamnionitis, use of antenatal steroids and magnesium sulfate), delivery room interventions (deferred or delayed cord clamping, cesarean section, optimal thermal management techniques), neonatal (brain protection bundle of care), infantile period (early identification of high-risk infant, use of brain imaging, general movements assessments, neurodevelopmental screening such as Bayley's scales, ages and stages questionnaire, and initiation of early intervention) and beyond (disability limitation and supportive measures by screening for neurosensory impairments and correcting them). In this article, we discussed and reviewed the evidence of the major



Figs 2A and B: Strategies for successful implementation of care bundles. The need for platelet transfusions should be evaluated in infants with severe thrombocytopenia

neuroprotective bundles of care during the neonatal period. There is wide variation in perinatal bundles used for extremely premature neonates, differences in gestational ages and rates of follow-up, the developmental assessment tools used, and recommendations for best practices with good external validity. Pooling of data is recommended even with such variations for direct comparisons and benchmarking, and successful harmonization to allow the study of rarer complications. Interventions can potentially directly impact brain injury (hemodynamic and respiratory management) or indirect impact (light, noise, thermoregulation, handling, and vascular access). The success of getting good institutional results depends mainly on staff awareness of the risk factors and bundle elements, and compliance with these GM-IVH bundles. It is important to focus on sustaining the neuro-bundle to achieve a consistently improved quality of care. The potential for continuous improvement should inspire us all.[270]

Tables 2 to 4 summarize the information provided to standardize the interventions to reduce the incidence and severity of GM-IVH.

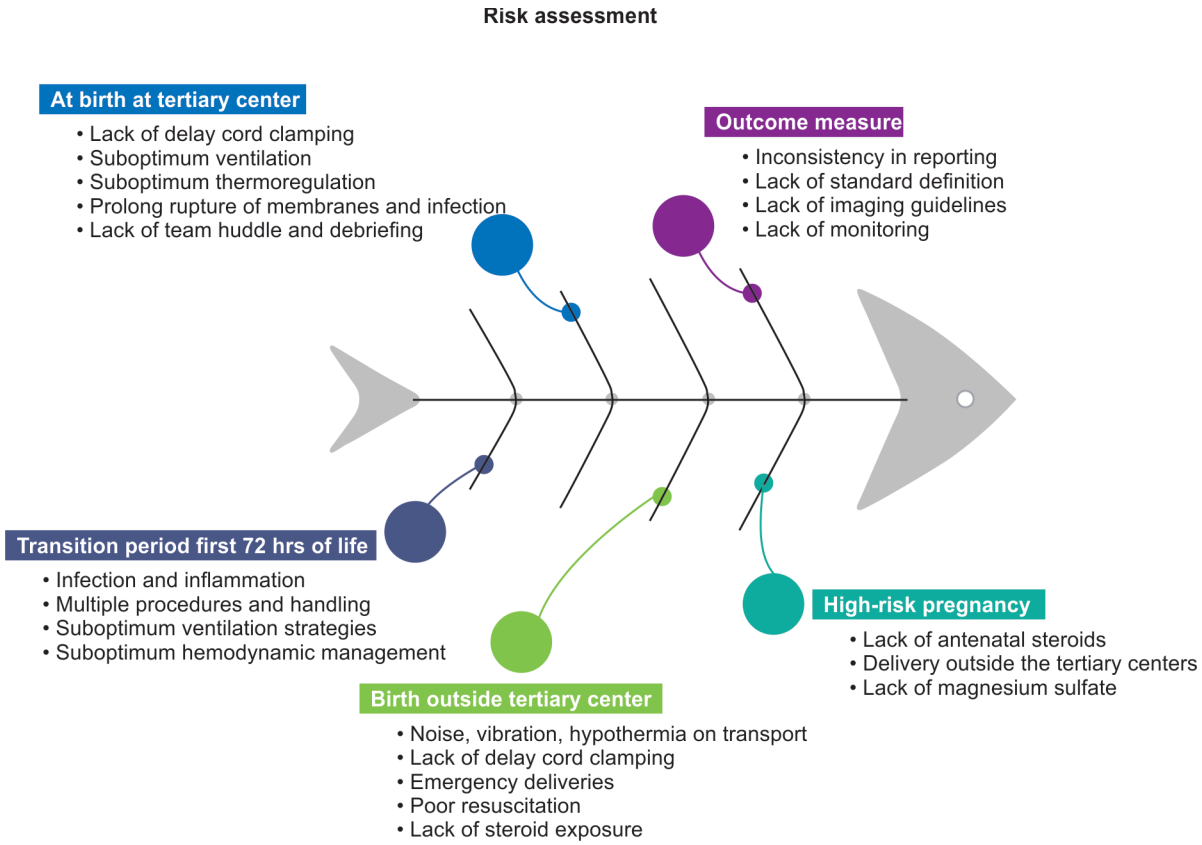


Fig. 3: Possible risk factors for GM-IVH based on postnatal age. Thrombocytopenia and coagulopathy are not included in this figure, as these factors are not specific to neonates and can increase the risk of intracranial hemorrhage in all age groups

Table 2: Strategies to improve standardization of GM-IVH care bundle

Antenatal care	• The *in-utero* transfer is always ideal.
	• Routinely administering antenatal corticosteroids 24 hours to 7 days before birth to all mothers expected to deliver a premature infant ≤ 34^{+6} and more than 22^{+6} weeks GA while those between 35 and 36^{+6} weeks GA in select clinical situations
	• Consider magnesium sulfate for all women experiencing imminent preterm delivery (≤ 33 + 6 weeks GA)
	• Outreach program
Perinatal care	• Golden hour
	• Delay cord clamping
	• Infants are managed on primary CPAP in the delivery room (except for infants born at <24 weeks' gestation)
Patient positing	• Maintain a neutral head position (head/neck in alignment with the body) when the infant turns and positions
	• Tilt the incubator to achieve 20–30º of upper body elevation during the first week of life
	• Avoid the baby's prone position during the first 72 hours of life
	• Avoid extreme 90º head turning
Nursing care	• Always question the necessity of care procedures
	• Experienced nurses must perform nursing care during the first week of life
	• Minimal handling with prioritizing the needs of the infant
	• Minimize routine care
	• Cluster care: Doing as much as tolerated by the infant (diaper changes, feeding, repositioning, etc.) at one time to allow the infant to have enough time for rest/sleep
	• Measure weight on admission and the fourth and seventh day of life
	• No length measurement for at least the first 72-hours
	• Nursing care and medical procedures should be combined and adapted to the infant's sleep-wake cycle
Care procedures	• Closed suction systems should be used on mechanically ventilated infants
	• The most experienced staff member must perform endotracheal intubation

(Contd...)

Table 2: *(Contd...)*

	• The blood samples from arterial lines with subsequent flashing should be drawn slowly • Avoid stress and pain • Evaluate stress and pain using pain scales • The first cranial ultrasound is better to be deferred at the end of the first week of life
Respiratory management	• Intubation should be selected based on clinical indicators according to the unit policy • Minimize extubation failure in the first 72 hours of life by ensuring that the baby meets extubation criteria outlined by the unit guidelines • Use volume target ventilation using an optimal lung strategy
Hemodynamic management	• Avoid inotropes if possible (allow for physiologic low blood pressure during first 72 hours from birth transition) • Have a clear guideline for when you use inotropes • Routine targeted neonatal echocardiography is not recommended in the first 72 hours unless intubated infant (ideally 24–48 hours), and there is concern for hemodynamically significant PDA
Thrombocytopenia and/or coagulopathy	• Need correction; target thresholds are still unclear—a balance between the lowest risk of bleeding and the minimum risk of inflammation. Further study is required

Table 3: Grade description for quality of evidence

Summary of recommendations with evidence

Grade	*Description of evidence*	*Certainty of evidence*
A	Strong - consists of studies from strong research	High
B	Moderate - consists of studies with a strong research design, but there are inconsistencies in results, generalizability, and/or risk/bias.	Moderate
C	Weak - studies show inconsistent results, and serious concerns about conclusions, generalizability, and/or risk/bias exist.	Low
D	A conclusion is either not possible or limited: Evidence is unavailable/or is of poor quality, and/or is contradictory.	Very low

Table 4: Summary of recommendations

Recommendation	*Description*	*Grade*	*Quality of evidence*
Antenatal steroid	Administration of antenatal corticosteroids to all the mother's expectant of delivery $\leq 34^{+6/7}$ weeks of gestation	B	II
Magnesium sulfate	Consider intrapartum magnesium sulfate for mothers who are at risk for imminent delivery of an infant $\leq 33^{+6}$ weeks GA in the next 24 hours	B	II
Delay cord clumping	Delayed umbilical cord clamping is recommended in preterm neonates	A	Ia
Mode of ventilation	Lung protective ventilation, which includes volume-targeted ventilation, should be the preferred mode of ventilation for all preterm infants during the first 72 hours of life	A	Ia
Head positioning	It should be neutral or in the midline during the initial 72 hours of life, along with the head of the bed raised to 20–30°	C	V
Nursing care	Nursing care during the first week of life must be performed by experienced nurses Minimal handling with prioritizing the needs of the infant Minimize routine care Measure weight on admission and the fourth and seventh day of life No length measurement for at least the first 72 hours	C	V
Care procedures	Closed suction systems should be used on mechanically ventilated infants Endotracheal intubation must be done by the most experienced staff member Drawing the blood samples from arterial lines with subsequent flashing should be drawn slowly	C	IIIa
Hemodynamic management	Avoid inotropes to treat hypotension unless a combination is associated with other signs, such as elevated lactate, prolonged capillary refill time, decreased urine output, or low cardiac output Care should avoid iatrogenic causes of hypotension, such as lung hyperinflation or dehydration Prophylactic indomethacin should be targeted to high-risk, extremely preterm infants, and the decision to treat should be based on combined risk factors	B	II

(Contd...)

Table 4: *(Contd...)*

Recommendation	*Description*	*Grade*	*Quality of evidence*
Umbilical cord milking	It is not recommended in very preterm infants <28 weeks due to increased risk for severe intraventricular hemorrhage	A	II
Platelet transfusion	It recommended a restrictive "low platelet" approach. Overall, there is limited effectiveness of platelet transfusions in reducing bleeding risk	A	II

***Quality of evidence classified as:**

- I: Systematic review with meta-analysis of homogenous randomized controlled trials (RCTs)
- II: Well-designed RCTs meta-analysis of non-homogenous RCTS
- III: Cohort or quasi-experimental trials
- IV: Descriptive
- V: Expert opinion or consensus

Additional lower-case letters are used: a: good quality, and b: lesser quality.

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