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Protecting the brain of the micropreemie

S.M. Boyd [a,b], S.J. Tapawan [c,d], N. Badawi [a,e], H. Popat [a,b,f,*]

[a] Grace Centre for Newborn Intensive Care, The Children's Hospital at Westmead, Sydney Children's Hospitals Network, Sydney, Australia
[b] Specialty of Child & Adolescent Health, Sydney Medical School, Faculty of Medicine & Health, The University of Sydney, Sydney, NSW, Australia
[c] Newborn Care Centre, The Royal Hospital for Women, Sydney, Australia
[d] School of Women's and Children's Health, University of New South Wales, NSW, Australia
[e] Cerebral Palsy Alliance Research Institute, Specialty of Child & Adolescent Health, Sydney Medical School, Faculty of Medicine & Health, The University of Sydney, Sydney, NSW, Australia
[f] NHMRC Clinical Trial Centre, Medical Foundation Building, Camperdown, NSW, Australia

A B S T R A C T

Advances in perinatal care have seen substantial improvements in survival without disability for extremely preterm infants. Protecting the developing brain and reducing neurodevelopmental sequelae of extremely preterm birth are strategic priorities for both research and clinical care. A number of evidence-based interventions exist for neuroprotection in micropreemies, inclusive of prevention of preterm birth and multiple births with implantation of only one embryo during in vitro fertilisation, as well as antenatal care to optimize fetal wellbeing, strategies for supporting neonatal transition, and neuroprotective developmental care. Avoidance of complications that trigger ischemia and inflammation is vital for minimizing brain dysmaturation and injury, particularly of the white matter. Neurodevelopmental surveillance, early diagnosis of cerebral palsy and early intervention are essential for optimizing long-term outcomes and quality of life. Research priorities include further evaluation of putative neuroprotective agents, and investigation of common neonatal interventions in trials adequately powered to assess neurodevelopmental outcome.

1. Introduction

Survival without disability has improved dramatically in recent years for infants born extremely preterm [1]. Although rates of cerebral palsy (CP) are declining in this group [2], there remains a significant burden of neurodevelopmental impairment (NDI) amongst surviving infants [3,4]. The greatest vulnerability to morbidities associated with preterm birth, including neurological sequelae, is observed in 'micropreemies' born at <24 weeks of gestation or <450 g birth weight. Prevention of injury to the developing brain in these tiniest infants is thus a significant focus of both research and clinical care within neonatology. A number of interventions exist for protecting the brain of the micropreemie, around which a strong evidence base has developed. These include antepartum administration of both corticosteroids for lung maturation [5] and magnesium sulfate for neuroprotection [6] in anticipation of preterm birth, as well as senior clinician attendance at delivery, which should occur wherever possible at a center with an on-site neonatal intensive care unit (NICU) [7]. The role of obstetric and midwifery leaders in preventing avoidable preterm births has also garnered attention, with successful education programs recently published focused on both clinicians and the broader community [8–10] and a shift towards implantation of only one embryo during in vitro fertilisation [11]. From a neonatal perspective, the secular trend towards use of non-invasive respiratory support strategies for preterm infants, including in the delivery room, is well-documented [12,13]. This represents a cultural paradigm shift away from a 'hands-on' resuscitation-based approach and towards supporting transition of preterm infants, inclusive of delayed or physiological-based cord clamping, investigation of less invasive means of delivering surfactant, and promotion of early skin-to-skin care. Targets for oxygenation both at the time of birth and in the NICU have also evolved in line with recent evidence [14,15].

Other aspects of early postnatal management are also important for optimizing brain growth and protecting against cerebral injury. Avoidance of the ischemic and inflammatory cascade accompanying sepsis and necrotizing enterocolitis (NEC), and the white matter injury (WMI) associated with these pathologies, is an increasingly established strategy for protecting against preterm neurological insult [16]. Early institution of enteral nutrition [17], optimization of postnatal growth [16], caffeine for apnea of prematurity [18] and pre-symptomatic treatment of the hemodynamically-significant patent ductus arteriosus [19] are all considered potentially neuroprotective. Attention is also increasingly

* Corresponding author. Grace Centre for Newborn Intensive Care, The Children's Hospital at Westmead, Sydney Children's Hospitals Network, Sydney, Australia.
E-mail addresses: Stephanie.boyd@health.nsw.gov.au (S.M. Boyd), Sarahjane.tapawan@health.nsw.gov.au (S.J. Tapawan), Nadia.badawi@health.nsw.gov.au (N. Badawi), Himanshu.popat@health.nsw.gov.au (H. Popat).

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being paid to the environment in which preterm infants develop ex-utero [20]. Noxious stimuli, such as pain, stress, noise, sleep disruption and adverse caregiver interactions may all modulate injury to the vulnerable preterm brain, and strategies to develop neurodevelopmentally supportive care are being incorporated into standard NICU practice [20]. Several additional potentially neuroprotective strategies show promise in the research domain, such as near infra-red spectroscopy (NIRS), erythropoietin and use of stem cells, for which the results of ongoing clinical trials are awaited. The importance of parents and caregivers in supporting and promoting infant development and the potential to modify clinical phenotype after preterm brain injury are deserving of mention. Screening using evidence-based tools during the neonatal period and early infancy [21], together with opportunities for parent-led, clinician-supported early intervention have shown substantial benefit in reducing severity of later neurodevelopmental impairments, including CP [22]. There is also growing recognition of the impact of preterm birth on mental and physical health in adulthood [23]. The effects of preterm birth on children and their families throughout the lifespan underscores the need for longer term neurodevelopmental and neuropsychiatric follow-up, in addition to developmental testing during infancy and early childhood.

2. Brain injury in preterm infants

Brain injury in preterm infants is complex and multifactorial. WMI is one of the most common forms of preterm brain injury and increases the likelihood of adverse neurodevelopmental outcomes [16,24]. While cystic periventricular leukomalacia (cPVL), a severe form of WMI, has become less prevalent with improvements in neonatal care [25], widespread adoption of MRI has enabled increased recognition of the full spectrum of neonatal white matter abnormalities [26]. Punctate white matter lesions, best visualized on MRI during the first week after birth, are increasingly recognized as a predominant lesion affecting preterm infants [27]. Extremely preterm infants with grade II-III intraventricular hemorrhage (IVH) and those who were more unwell have been identified as being at particular risk [26]. Like cPVL, periventricular hemorrhagic infarction, a complication of IVH, is associated with later neurodevelopmental impairment amongst very preterm-born children [28]. A requirement for shunting for treatment of post-hemorrhagic hydrocephalus complicating IVH is likewise associated with adverse neurodevelopmental outcomes [29]. A significant reduction in rates of severe IVH has been observed internationally in recent years [30–32]. This is likely to be attributable to improvements in perinatal care, particularly at earlier gestations, and it is hoped this will translate into reduced rates of CP when outcomes of this birth cohort are reported.

Consistent with findings of greater risk amongst the sickest infants, exposure to systemic illness and its treatments during the neonatal period is thought to be injurious to the developing white matter and is implicated in the pathogenesis of WMI [33–38]. Complications of prematurity, and in particular those that have an inflammatory component, such as NEC, sepsis and bronchopulmonary dysplasia (BPD), are clearly associated with microstructural brain changes, mainly of the white matter [34,35,37–41]. The white matter in preterm neonates is particularly susceptible to hypoxia-ischemia [16], and it is the combination of ischemia and inflammation that appears to mediate development of WMI [16]. The clinical course of the preterm neonate may even be more significant determinant of white matter development and brain injury than the degree of prematurity [42,43], and importantly, is potentially modifiable. Current evidence-based interventions for neuroprotection in micropreemies and areas for further research are summarized in Fig. 1.

3. Antenatal initiatives

Protecting the brain of the micropreemie starts during fetal life. Despite improved awareness of strategies to prevent preterm birth, prematurity and its associated morbidities remain a significant public health issue. A number of antenatal interventions have, however, been shown to reduce the incidence of preterm birth. These include: midwifery-led models of care, screening for infection, zinc supplementation (in the absence of systemic illness, with evidence of a 14% relative reduction in preterm birth mainly in women of lower socioeconomic status) [44], and cervical cerclage for women with singleton pregnancies at high risk of preterm birth [45]. Low-dose aspirin early in pregnancy is effective in reducing pre-eclampsia, fetal growth restriction, and preterm birth associated with these complications [46]. A number of jurisdictions have also successfully demonstrated reductions in preterm births using a combination of education and clinical initiatives targeting both health professionals and the general public [8–10]. These should

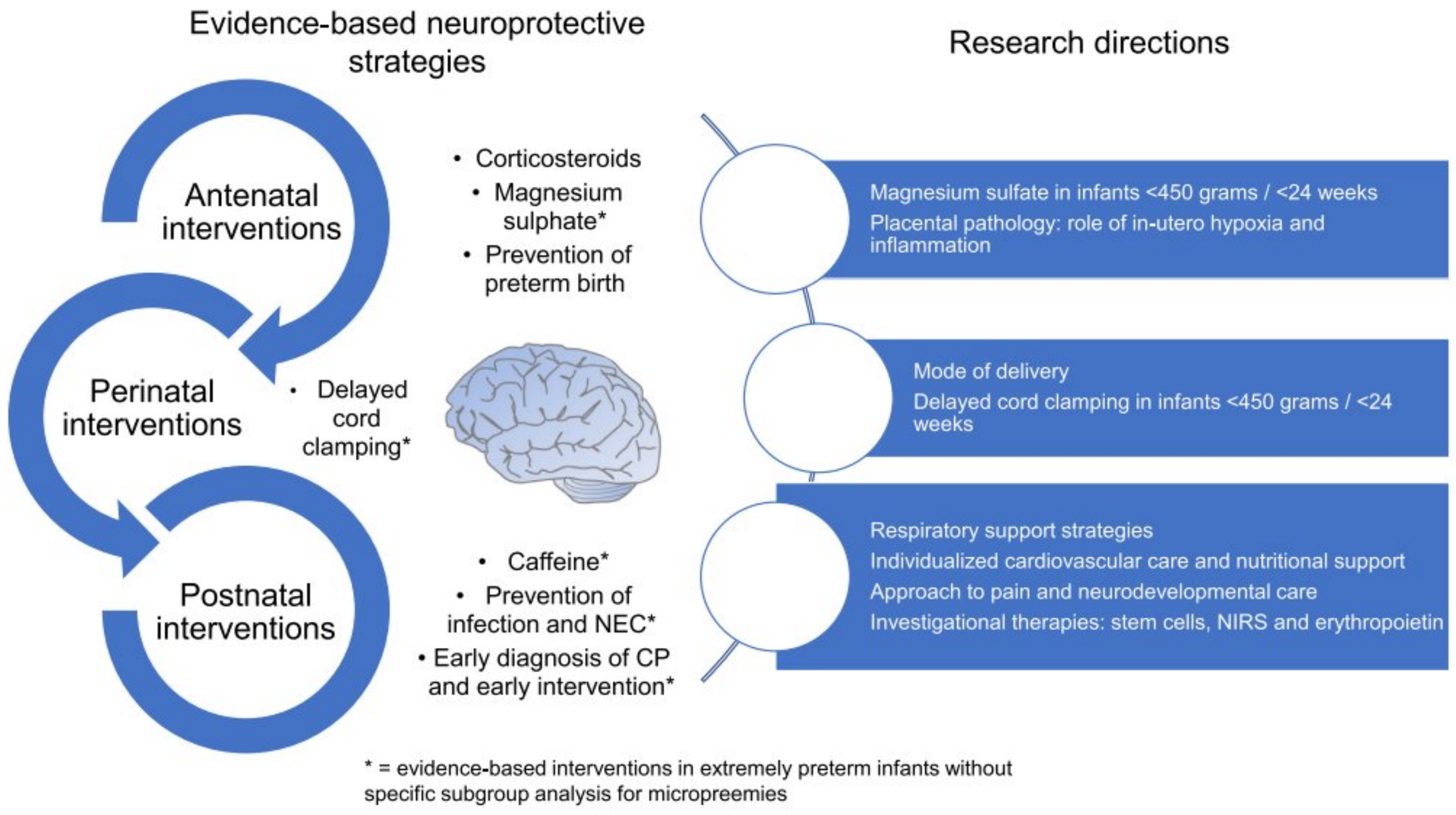

Fig. 1. Evidence-based strategies for neuroprotection in micropreemies and future research directions.

continue to be supported and expanded to wider populations given demonstrated benefit in reducing rates of prematurity. Community-based programs have also been utilized successfully for population groups with high rates of adverse health outcomes, such as Aboriginal and Torres Strait Islander individuals [47].

When preterm birth is inevitable based on fetal and/or maternal indication, it is crucial to optimize fetal health and wellbeing prior to and during transition to neonatal life. This is particularly pertinent for the smallest and most vulnerable infants; the micropreemies. Postnatal infection has been strongly implicated in WMI, although evidence for the role of antenatal infection has been less consistent [16]. Whilst chorioamnionitis has historically been associated with abnormalities of white matter development and adverse neurological outcomes, more recent MRI studies have not demonstrated an increased risk of WMI with histologically-confirmed chorioamnionitis [48,49]. A 2017 meta-analysis found, however, that preterm histological chorioamnionitis may be a risk factor for later CP, which was not the case for term infants [50].

Intrauterine growth restriction (IUGR) is multifactorial, and is associated with an increased risk of NDI, cerebral palsy and death [51, 52]. IUGR is associated with both chronic intrauterine hypoxia [53] and an elevated risk of hypoxia-ischemia at birth due to reduced tolerance of the transition to extrauterine life. Early diagnosis is important for identification of the cause of IUGR, monitoring of fetal wellbeing and decision-making around timing of delivery. The role of placental health in modulating brain development and infant outcomes continues to be explored [54,55], and assessment of the role of both placental insufficiency and severe fetal inflammatory response may be helpful in this regard.

3.1. Antenatal corticosteroids

Antepartum administration of corticosteroids has demonstrated significant and consistent benefits for outcomes of extremely preterm infants [56], and is considered a standard prophylactic treatment where there is a high risk of preterm birth [57]. In addition to the established beneficial effects on lung maturation [5], corticosteroids are postulated to promote maturation of the germinal matrix microvasculature, reducing risk of IVH [58]. In the longer term, a reduced risk of death or neurodevelopmental delay at 18–22 months for infants born at 23–25 weeks has been observed following antenatal corticosteroid treatment [59]. Favorable effects on rates of NEC and early-onset systemic infection [56] may provide additive neurodevelopmental benefit, and advantages may be greatest in the most extremely preterm patient group. A systematic review of observational data reported a nearly 50% decrease in the odds of death to discharge (odds ratio [OR], 0.48; confidence interval [CI], 0.38 to 0.61) in 3646 neonates less than 24 weeks' gestation exposed to corticosteroids antenatally. There was no subgroup analysis based on birthweight [60]. In 2020, a Cochrane review of 27 randomized trials including 11, 925 neonates showed similar beneficial effects in reducing risks of perinatal death (RR, 0.85; 95% CI, 0.77 to 0.93), neonatal death (RR 0.78; 95% CI, 0.70 to 0.87) and RDS (RR, 0.71; 95% CI, 0.65 to 0.78), without increasing important maternal morbidities or mortality [61]. Importantly, this review included 10 trials from low or middle-income countries, where resource limitations can hamper efforts to reduce complications of preterm birth.

Evidence in micropreemies: Retrospective data from the Neonatal Research Network of Japan (NRNJ) reported 55% (811/1473) survival to hospital discharge amongst infants with a birth weight of <500 g. Exposure to antenatal corticosteroids was a significant survival factor; that is, 51% of surviving NICU graduates were exposed to compared with 37% of non-survivors ($p < 0.01$) [62].

3.2. Magnesium sulfate

Intravenous use of magnesium sulfate ($MgSO_4$) intrapartum offers an inexpensive and useful neuroprotective effect in decreasing prematurity-related neurodevelopmental impairment, including CP. Although its biological mechanism is unclear, it is postulated that $MgSO_4$ has anti-inflammatory properties [63], blocks the *N*-methyl-d-aspartic acid (NMDA) receptors to stop nerve cell damage [64], dilates human uteroplacental resistance vasculature [65], and prevents reperfusion injury by early vascular stabilization [66]. A Cochrane systematic review in 2009 reported a neuroprotective effect of $MgSO_4$, with a 32% relative risk reduction in CP (RR, 0.68; 95% CI, 0.54 to 0.87) and a significant reduction in the rate of substantial gross motor dysfunction (RR, 0.61; 95% CI, 0.44 to 0.85) amongst infants whose mothers received the drug intrapartum [6]. Despite recommendations and clinical guidelines on the use of $MgSO_4$ for fetal neuroprotection [67,68], significant gaps exist in its integration into clinical practice. An Australian study analysing usage of $MgSO_4$ in babies born at 23–27 weeks' gestation – the group for whom benefit has been shown to be greatest – reported only 68% were exposed to $MgSO_4$ antenatally [69]. A European cohort study reported only 9 out of 119 (7.6%) maternity centers had a policy of using $MgSO_4$ at <32 weeks' gestation for neuroprotection [70]. These data underscore the role and importance of implementation science to improve the uptake of this important perinatal intervention.

Evidence in micropreemies: Current trials on $MgSO_4$ treatment do not provide separate data on micropreemies. Further research on neuroprotective benefit of $MgSO_4$ is warranted as active resuscitation at lower gestational thresholds is increasingly offered.

4. Perinatal care

4.1. Place of birth and presence of senior staff

Worldwide regionalization of perinatal care has been implemented in recognition of the advantages to the developing preterm infant: there is clear evidence that extremely preterm infants born where there is a co-located, specialised neonatal facility have better outcomes [[7,71–73]]. This includes lower odds of death, severe neurodevelopmental impairment and CP [71]. The best way to ensure this is for transfer to occur prior to birth ("in utero"), with delivery of "inborn" infants. Ex-utero transfer and "outborn" delivery of high-risk micropreemies can delay provision of critical neonatal intensive care support during the perinatal transition period; late (>48 h) postnatal transfer appears to be particularly deleterious [74]. It remains challenging, however, to predict the likelihood of imminent preterm birth in the retrieval context [75]. Efforts to improve logistics and care coordination by centralising specialist retrieval service providers has the potential to streamline both the referral and transfer process. Holistic care also includes provision of emotional and financial support to end-users who may be abruptly relocated to an unfamiliar environment during an already stressful situation [76].

Clinical guidelines for neonatal resuscitation in tertiary perinatal units recommend that deliveries of preterm neonates <26 weeks should be attended by the most experienced healthcare practitioner, preferably a consultant neonatologist, who is trained in resuscitation [77,78]. Every effort should be made to ensure senior neonatal clinicians are available to attend deliveries of micropreemies, as there is likely to be benefit to the infant in terms of both procedural expertise and 'human factors' management. A national survey in the UK on delivery room management in very preterm infants (<32 weeks) by Singh et al. in 2013 reported 119 units (63%) routinely ensure out-of-hours consultant attendance at very preterm births, however the threshold gestation varied between units. The gestation thresholds were not specified and no weight threshold was reported. There was a significant difference in routine neonatologist attendance between tertiary and non-tertiary units (82% vs. 55%, $P < 0.01$). The effect of senior staff presence on outcomes of micropreemies has not been rigorously studied, however, and requires prospective validation.

Evidence in micropreemies: There are no data on the rate of attendance of senior staff at delivery of micropreemies specifically, nor impact of senior staff attendance on neurodevelopmental outcome.

4.2. Mode of delivery

Choosing the optimal and safest mode of delivery for preterm birth remains controversial. Although there is theoretical advantage to caesarean section over vaginal birth in singleton preterm infants, this has not universally translated to improved neonatal outcomes [79]. A population-based study of 2094 livebirth preterm infants <28 weeks reported that vertex vaginal birth did not increase mortality [80]. Conversely, a study of a smaller cohort of 397 infants <1,251 g reported a strong association between vaginal delivery and PVL in surviving infants (5% versus 1%; OR, 11.5; 95% CI, 1.66 to 125) [81]. A recent systematic review and meta-analysis demonstrated a reduced adjusted odds of death in extremely preterm vertex infants <28 weeks (adjusted odds ratio [aOR], 0.62; 95% CI, 0.39 to 0.99) with caesarean section [82], though cautioned that randomized trial evidence is lacking. The maternal risks associated with caesarean section at early gestations should also be considered. Well-designed prospective studies are necessary to fully investigate the effect of mode of delivery in extremely preterm births.

Evidence in micropreemies: Currently, there is no conclusive evidence that a particular delivery method for infants <450 g improves brain outcomes.

5. Early postnatal care and cardiorespiratory support

5.1. Delayed cord clamping

There is increasing recognition of the importance of the perinatal transition period in moderating rates of complications during admission and brain injury risk and for preterm infants. Immediate cord clamping imposes additional physiological stress for the transitioning preterm infant, resulting in a rapid reduction in cardiac venous return by 30–50% [83]. This fall in venous return reduces cardiac preload and compounds the negative effects of increased afterload on the transitioning preterm heart, causing a reduction in arterial blood pressure and cardiac output [83]. Additionally, cerebral blood flow increases initially and then rapidly decreases as cardiac output falls [84]. Conversely, delaying cord clamping until after respiration and pulmonary blood flow are established allows for preservation of venous return and support of left ventricular preload and cardiac function during transition [84]. Delayed cord clamping of at least 60 s has been shown to reduce hospital mortality (RR, 0.73; 95% CI, 0.54 to 0.98) [85] and the risk of death or major disability by 17% (RR, 0.83; 95% CI 0.72 to 0.95) at 2 years of age [86] and is recommended routinely for extremely preterm infants. However, rather than delaying cord clamping for an arbitrary period of time ('delayed cord clamping'), initiation of respiratory effort may be a better indicator for appropriate timing of cord clamping to facilitate smooth cardiorespiratory transition ('physiological based cord clamping') [83]. Physiological based cord clamping recognizes that the benefits observed in trials of delayed cord clamping in preterm infants are likely to be predominantly driven by maintenance of transitional cardiac function, rather than a result of red cell transfusion [87]. 'Milking' of the umbilical cord should be avoided due to randomized controlled trial (RCT) evidence of increased IVH at extremely preterm gestations (risk difference [RD], 16%; 95% CI, 6%–26%) when compared with delayed cord clamping [88].

Evidence in micropreemies: There is no subgroup analysis in existing systemic reviews addressing the question of delayed cord clamping in micropreemies. Delayed cord clamping >60 s is recommended in the micropreemie unless evidence emerges to the contrary. Milking of the umbilical cord should be avoided unless further evidence is available showing benefit.

5.2. Respiratory support

There remains uncertainty regarding optimal oxygen concentrations for resuscitation of preterm infants [89]. Whilst the starting oxygen concentration in the delivery room continues to be refined, not achieving an oxygen saturation of 80% at 5 min of age is associated with adverse outcomes, including IVH [14]. This is a useful metric during initial oxygen titration, though achieving the desired SpO_2 of 80–85% at 5 min of age is challenging [14]. Oxygen saturation targets during NICU admission have also been investigated, since both hypoxemia and hyperoxemia have been associated with increased risks of sequelae after preterm birth [90]. Hypoxemic episodes have been linked with late neonatal deaths and NDI [91], and there are animal data suggesting that hyperoxia may result in white matter damage [92,93]. An individual patient data meta-analysis of lower (85–89%) versus higher (91–95%) oxygen saturation target ranges for preterm infants did not find a difference in death or disability at 18–24 months between the two groups, though there was an association between the lower target range and a higher risk of death and NEC, with a lower risk of treatment for retinopathy of prematurity (ROP) [15]. Attempts have been made to create a 'closed-loop' system for maintaining oxygen saturations within the target range in extremely low gestational age infants, with the goal of ameliorating the risks associated with hypoxemia and hyperoxemia [94]. Results of a trial assessing effects on relevant clinical outcomes (NCT03168516) are awaited [90].

BPD is an important risk factor for disturbances of white matter development and adverse neurodevelopmental outcomes [39,95]. Use of positive pressure ventilation (PPV) in the delivery room has been associated with severe IVH [96], and there is good evidence of the benefits of initiation of respiratory support in preterm infants with continuous positive airway pressure (CPAP) rather than intubation. This includes a reduction in the combined outcome of death or BPD [12], although this finding has not been universal [97]. Non-invasive positive pressure ventilation (NIPPV) reduces the incidence of extubation failure and the need for re-intubation within 48 h to one week more effectively than CPAP; however, it has no effect on chronic lung disease nor on mortality [98]. Due to limited data and very low certainty evidence, it is not possible to determine if diaphragm-triggered non-invasive respiratory support is effective or safe in preventing respiratory failure in preterm infants [99]. Prolonged mechanical ventilation is associated with abnormalities of white matter development and lower motor scores at preschool age [100]. In addition, the link between hypocapnia in the first few postnatal days and subsequent development of PVL has been widely reported [101–103]. As such, permissive hypercapnia has become a broadly adopted strategy for both lung- and neuroprotection, although evidence of improved outcomes is currently lacking [104,105].

In attempts to avoid mechanical ventilation and its associated risks, efforts have been made to deliver surfactant therapy less-invasively. These include administration of surfactant via thin catheter, known as minimally invasive surfactant therapy (MIST) or less invasive surfactant therapy (LISA). A recent Cochrane review of 16 studies demonstrated a reduced risk of death or BPD with surfactant administration via thin catheter (RR, 0.59, 95% CI, 0.48 to 0.73; number needed to treat to prevent death or BPD in one infant 9), as well as less intubation within the first 72 h and a reduced incidence of both major complications and in-hospital mortality [106]. Unfortunately, none of the included studies reported on the outcome of death or survival with NDI, and this is an area for potential further research.

Evidence in micropreemies: None of the trials of oxygen concentrations for resuscitation at birth, oxygen targeting during the NICU stay, respiratory support with CPAP or NIPPV, or administration of surfactant via thin catheter have reported separately on micropreemies.

5.3. Respiratory treatments

Caffeine, administered to preterm infants for prevention and

treatment of apnea of prematurity, has been explored for its potential neurodevelopmental benefits. The Caffeine for Apnea of Prematurity (CAP) trial showed improved survival without neurodevelopmental disability at 18–21 months of age with caffeine treatment [18], and in follow-up at 11 years of age was associated with a reduced risk of motor impairment in children born with very low birth weight [107]. Timing of administration may also be important. A cohort study of 2108 infants born at <29 weeks demonstrated reduced rates of severe neurologic injury in infants receiving caffeine 'early' (within 2 days of birth) rather than 'late' [108].

Early (<7 days) dexamethasone treatment in preterm infants is associated with a significant increase in the risk of CP (RR, 1.77; 95% CI, 1.21 to 2.58) [109]. This risk is not observed with late (≥7 days) treatment, which reduces the risks of mortality and BPD, although studies have not been powered to detect adverse long-term neurodevelopmental outcomes [110]. In infants at higher risk of BPD, postnatal corticosteroid treatment has been shown to increase survival without CP in a meta-regression using data from 20 randomized controlled trials [35]. As such, benefits are likely to outweigh risks for use of corticosteroids ≥7 days in infants who are unable to be weaned from mechanical ventilation [110], who are at a higher risk of BPD and likely to be at increased risk of neurodevelopmental impairment.

Evidence in micropreemies: Trials of caffeine therapy and dexamethasone treatment do not provide separate data on micropreemies.

5.4. Cardiovascular care

Low systemic blood flow has been identified in up to 35% of transitioning preterm neonates using cardiac ultrasound [111], and is a risk factor for adverse short- and long-term outcomes in these infants [112]. Effective cerebral autoregulation occurs in preterm infants within only a narrow range of blood pressure fluctuation [113], and infants less than 26 weeks are at particularly high risk of pressure-passive cerebral circulation [114]. Treatment to improve numerical blood pressure – which is poorly correlated with cardiac output and end-organ perfusion – has not been shown to improve outcomes [115]. There is also a risk of contributing to the ischemia-reperfusion injury implicated in the pathogenesis of IVH where cerebral circulation is pressure-passive [114, 116]. Preterm infants with pre-symptomatic PDA receiving targeted treatment based on cardiac ultrasound parameters have been shown to be less at risk of IVH and pulmonary hemorrhage [19], although improvement in long-term outcomes, including neurodevelopment, has not been demonstrated. There is limited evidence of improved outcomes to guide cardiovascular care of extremely preterm neonates, and a number of treatments may be associated with more harm than good. An individualized approach based on assessment of underlying pathophysiology may be helpful, although requires prospective validation.

Evidence in micropreemies: A higher rate of PDA has been observed at 23–24 weeks (93%) than in older gestational age groups [117], with reduced efficacy of ibuprofen for ductal closure observed at 23–26 weeks when compared with infants born at 27–30 weeks of gestation [118]. Less frequent spontaneous PDA closure has also been observed in the most extremely preterm and low birthweight infants [119]. In addition, PDA treatment has not been shown to reduce neurodevelopmental impairment [120], including in micropreemies, and surgical PDA ligation has been associated with NDI in a cohort study of extremely preterm neonates with birth weight ≤500 g [121]. Large trials that specifically include infants at highest risk of PDA-related morbidity and minimize rates of open label treatment are recommended [120] to better understand the potential for neuroprotective benefit amongst the most extremely preterm infants.

There is no evidence of improved neurodevelopmental outcomes amongst infants <24 weeks of gestation related to their cardiovascular management, including specifically treatment of hypotension. Studies assessing preterm neonatal hypotension stratified by underlying pathophysiology may be useful in this regard.

6. Prevention of infection

Postnatal infection is a significant risk factor for WMI and childhood neurodevelopmental impairment [34–36]. Both clinical infection, and proven, culture-positive infection are believed to be detrimental to the developing brain [33]. There is also an association between the number of infections, brain dysmaturation and later impairment; infants experiencing ≥3 infections are considered to be at greater risk of poorer motor outcomes [33]. A 'two hit' model of injury has been proposed, with sensitization from initial infection increasing brain injury risk with subsequent inflammatory and ischemic episodes [16,33]. This underscores the importance of infection prevention in the NICU, with bundles including strict hand hygiene practices and audits, central line care and antimicrobial stewardship [122] playing an important role in reducing infection-related mortality and morbidity, including brain injury. NEC, particularly when requiring surgical intervention, is also associated with WMI and impairments in cognitive and motor function [123]. Probiotics have been shown to reduce the risk of NEC [124], although have not currently been shown to confer neurodevelopmental benefit [125]. Similar to care bundles for prevention of sepsis, some centers have developed 'NEC prevention' toolkits, inclusive of prioritizing human milk feeding with maternal milk, adoption of a standardized protocol for enteral feeding, and additional strategies including a risk score [126]. Success of multimodal quality improvement strategies for NEC prevention require further investigation to assess potential impacts on rates of NEC and neurodevelopmental outcomes.

Evidence in micropreemies: Preterm premature rupture of membranes at 22–25 weeks' gestation has been associated with a high incidence of morbidity and mortality, including low rates of survival without CP in infants born at 22–23 weeks [127]. Late-onset sepsis is common amongst infants born at ≤24 weeks of gestation, occurring in 33% of infants born at 22–24 weeks in a cohort study of infants with a birth weight of <400 g [128] and in 20% of infants with a birth weight of ≤500 g in a Japanese study [62]. In a nationwide cohort study of infants <500 g in South Korea, sepsis rates were 38% amongst surviving infants, with infection and gastrointestinal disease identified as the two primary causes of death after the first postnatal week [129]. Data from the Neonatal Research Network of Japan indicated no change to rates of neurosensory impairment among infants born at ≤500 g over a 10-year period from 2003 to 2012, with rates of NDI and CP of 59% and 22.2%, respectively [121]. In this cohort, NDI was associated with severe IVH, cystic PVL, severe NEC, surgical ligation for PDA and male sex [121]. These data underscore the vulnerability of micropreemies to inflammation and associated white matter damage and the link between neonatal morbidities and subsequent neurodevelopmental impairment.

7. Nutrition and growth

The role of nutrition and growth in optimizing brain development is increasingly recognized [16]. Micropreemies experience a rapid period of brain growth and maturation during admission to the NICU and are uniquely susceptible to the effects of poor growth and nutritional deficits. A positive association has been identified between nutrition, weight gain and brain volumes, which in turn correlate with early neurodevelopment [130]. In addition, faster growth of head circumference –which is a proxy for brain growth – from birth to term age has been associated with improvements in IQ [131]. Optimizing early nutrition seems to be particularly important [132]. A number of advantages have been observed with enhanced caloric and macronutrient provision in the weeks following preterm birth, including increased developmental quotient [133] and improved language scores [134]. Higher lipid and energy intakes in the first 2 postnatal weeks have also been shown to correlate with improved MRI appearances using the Kidokoro scoring system for brain abnormalities [135]. Provision of enteral nutrition wherever possible appears to confer specific benefits. A prospective

observational ultrasound study of the relationship between energy intake and brain growth found significant differences based on whether nutrition was administered via the enteral or parenteral route [17]. High energy intake provided enterally was positively correlated with better cerebral growth on ultrasound than parenteral energy intake.

Nutritional interventions have not readily translated into neurodevelopmental benefit [136]. A retrospective analysis to determine optimal nutrition regimens in extremely preterm neonates identified that although postnatal protein intake appeared to be important for white matter development, this did not necessarily translate into improved long-term motor and cognitive outcomes [137]. Results of the ProVIDe trial investigating the effect of additional protein provision in the first 5 days after birth to infants with birth weight <1000 g demonstrated a negative neurodevelopmental effect at follow-up [138]. There is growing interest in the use of body composition as a tool for understanding and optimizing nutritional drivers of brain growth in preterm infants [139], and sex-specific differences in nutrition handling which are yet to be fully investigated [136]. These evolving areas of research may represent opportunities for a 'personalized medicine' approach to neonatal nutrition with the potential for improvements in outcomes.

Evidence in micropreemies: Growth velocity in the NICU in preterm infants of 500–1000 g birth weight exerted a significant effect on neurodevelopmental and growth outcomes at 18–22 months' corrected age in a multicenter cohort study [140]. Data addressing effects in micropreemies specifically are sparse, and various nutritional interventions in RCTs enrolling broader groups of preterm infants have not resulted in demonstrated neurodevelopmental benefit [141]. Further research into nutritional interventions for neuroprotection of micropreemies is warranted.

8. Neurodevelopmentally supportive care

8.1. Approach to pain

Exposure to painful procedures utilized in neonatal intensive care has been identified as having a negative effect on both brain maturation [43,142], and childhood motor and cognitive outcomes amongst preterm born infants [143]. Higher procedural pain and exposure to neonatal infection have been associated with reduced cerebellar volumes in infants born at 24–32 weeks, with smaller volumes of specific cerebellar regions related to poorer cognition and motor/visual integration [144]. Fewer skin breaks have also been associated with significantly larger thalamic volumes in early life in very preterm neonates [145]. Hormonal, behavioural and physiological disruptions are implicated [143], and cumulative procedural pain, irrespective of illness severity, appears to be particularly adverse [142,143]. Prevention and management of infant pain requires a proactive approach to screening and assessment. A large number of neonatal pain assessment tools exist [146], and those validated for use in newborns should be utilized in a standardized manner to guide pain relief, incorporating both non-pharmacological and pharmacological interventions as appropriate [146]. Skin-to-skin, direct breastfeeding (where developmentally possible), facilitated tucking, non-nutritive sucking and oral sucrose administration are all effective, evidence-based interventions for neonatal pain [146]. Other pharmacological treatments require a thorough risk-benefit assessment, as some, for example midazolam, have been associated with significant adverse events in preterm newborns, such as hypotension, IVH, PVL and death [147]. Analgesics that have generally not been associated with long-term sequelae when used appropriately, such as morphine, may still be associated with negative effects, such as prolongation of mechanical ventilation and time to attain full enteral feeds [147].

Evidence in micropreemies: No published analysis has been identified specifically addressing effects of pain or its treatments on infants born at ≤24 weeks or <500 g, and effects of procedural pain in the smallest infants likely to be exposed to the highest cumulative burden of neonatal pain represents a valuable future research opportunity.

8.2. Neutral head position

Head positioning in the early postnatal period has been explored for the possibility of neuroprotective benefit. It is hypothesized that lateral extremes of head position can partially occlude jugular veins, affecting venous drainage and causing a temporary increase in intracranial pressure [148]. Maintaining midline head positioning during the in the first 72 h has therefore been proposed as an IVH prevention strategy [149]. A recent systematic review concluded that this practice did not, however, significantly decrease the incidence of IVH, nor alter cerebral hemodynamics or oxygenation [150]. The role of early postnatal head positioning in reducing IVH is yet to be fully elucidated, however some centers opt for neutral head positioning based on potential benefits and a low risk of harm.

Evidence in micropreemies: There are no published clinical data to support this theoretical neuroprotective benefit, especially for micropreemies.

8.3. Neuroprotective developmental care

A focus on reduction of neurodevelopmental morbidity has led to interest in improving developmentally supportive care in the NICU [20]. Supporting closeness of infants and parents, early and prolonged skin-to-skin contact, availability of family rooms and a family-centered approach to care are considered worthwhile interventions for a neurodevelopmentally supportive NICU environment [20]. Early skin-to-skin care (SSC) in the first 72 h after birth for extremely low birth weight (ELBW) infants has been found to be feasible, without increasing IVH [151]. A retrospective study showed that early SSC for ELBW infants was also associated with increased intake of mother's own milk at discharge [152], in addition to well-established benefits for respiratory stability, glucose and temperature homeostasis, and exclusive breastfeeding rates at discharge amongst low birth weight infants [153]. The role of early SSC in unstable preterm infants requires further investigation, however, and an ongoing trial of the practice in unstable 28–32^{+6}-week infants is a sensible first step (IPISTOSS study - NCT03521310).

In addition to guidance with respect to parent-infant interactions, neuroprotective developmentally supportive care (NDSC) incorporates best practice recommendations regarding: the sensory environment, with a focus on ambient noise, unit design and cycled lighting, as well as attention to pain and stress, sleep, positioning, feeding practices, education and training and continuity in caregiving [20]. Use of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP), which has been shown to reduce length of stay, incidence of chronic lung disease and disability at 18 months corrected age [154] is suggested as a holistic developmental care model supporting integration of NDSC practices within the NICU [20].

Evidence in micropreemies: Predominant breast milk feeding in the first 28 days after birth has been associated with a greater deep nuclear gray matter volume at term equivalent age, as well as better intelligence quotient (IQ), academic attainment, working memory and motor function at 7 years of age in a cohort study of infants born at <1000 g [155]. Although evidence exists for several sensory-based interventions in the NICU from 25 to 28 weeks of gestation [156], in very preterm newborns <32 weeks [157] and in preterm infants 22–36 weeks [158], evidence specifically addressing benefits for micropreemies is less well-developed.

9. Investigative therapies

9.1. Stem cells

Accumulating evidence suggests that stem cells act in a paracrine

manner through the release of exosomes and/or anti-inflammatory, immunomodulatory and growth/neurotrophic factors. The possibility that stem cells could directly replace injured cells is still debated [159]. There are greater than 50 preclinical studies that have reported on use of stem cells in perinatal brain injury animal models, with one fourth using a preterm brain injury animal model. They all differ regarding the animal model used, type of stem cell, route of administration and time of treatment. Currently the most promising cell types are mesenchymal stem cells (MSCs) and umbilical cord blood stem cells (UCBSc). Of the 57 studies identified, most of them used MSC or UCBSc. However, the source of these cells varies greatly, with 12 clearly different sources identified. The one consistent feature across all the 57 identified studies is that they reported positive effects of stem cell treatment [159]. This would suggest selective reporting of positive results or potentially efficacious treatment.

Recently, a phase I clinical trial showed the safety and feasibility of UCB-MSC transplantation for severe intraventricular hemorrhage (IVH) in preterm infants. The study was performed by intraventricular injection of allogeneic UCB-MSCs in nine preterm infants with severe IVH, with a follow-up to 40 weeks of corrected age. The mean gestational age of the infants was 26.1 ± 0.7 weeks and birth weight 808 ± 85 g and the cells were administered at 11.6 ± 0.9 postnatal days. The outcomes indicated that UCB-MSC therapy was well tolerated with attenuated periventricular hemorrhagic infarct, and no infants suffered from dose-limiting toxicities or serious adverse reactions such as anaphylaxis or death within 6 h after injection [160]. Although the results were encouraging, randomized controlled clinical trials with long-term follow-up are necessary. There is a phase IIa randomized controlled study underway in 22 preterm infants evaluating the efficacy and safety of a single intraventricular administration of Pneumostem® (donor umbilical cord blood derived MSCs) for treatment of IVH in high-risk premature infants by comparing a Pneumostem-treated group with a control group (NCT02890953) [161]. Substantial responsibility rests upon the global neonatal community to collaborate and rigorously study this promising treatment with properly designed and adequately powered trials.

Evidence in micropreemies: There is no study reporting exclusively on micropreemies. One micropreemie (GA 25 wks and BW 440 g) was included in the phase one study evaluating the safety of intraventricular injection of allogeneic UCB-MSCs [160].

9.2. Near infra-red spectroscopy

Low regional cerebral oxygen saturation ($rScO_2$) immediately after birth is reported to be associated with periventricular hemorrhage (PIVH) [162,163]. Low $rScO_2$ in the first 48 h of life has been reported to be associated with death or PIVH [164]. $rScO_2$ persistently below 40% has been consistently reported to be associated with brain injury in clinical and pre-clinical studies [165–167]. Consistent with this observation, increased cerebral fractional tissue oxygen extraction (cFTOE) in the first few days of life has been reported to be associated with PIVH [168,169]. In addition to the regional cerebral oxygenation, impaired cerebral autoregulation has been inconsistently reported to associated with cerebral injury in preterm infant, with some studies reporting such an association [170–172] and others not reporting such an association [173–175].

There have been two randomized trials of NIRS oximetry in extremely preterm infants; one in the context of resuscitation after birth and the other in the first three days of life. The pilot randomized trial on 60 infants less than 34 weeks' gestation using cerebral NIRS oximetry to influence respiratory support and supplemental oxygenation administration after birth revealed reduction in the burden of cerebral hypoxia in the group with NIRS oximetry [176]. The other randomized controlled trial (SafeBoosC trial) included 166 infants less than 28 weeks' gestation randomized to cerebral NIRS oximetry and a dedicated algorithm or blinded NIRS oximetry with standard management in the first three days of life. This study revealed a reduction in the burden of hypoxia and hyperoxia in the group with NIRS oximetry and a dedicated algorithm. The two groups did not differ in any of the clinical outcomes [177].

The SafeBoosC-III trial (phase III trial) is investigating the benefit and harms of treatment based on near-infrared spectroscopy monitoring compared with treatment as usual. The hypothesis is that treatment based on near-infrared spectroscopy monitoring for extremely preterm infants during the first 72 h of life will result in a reduction in severe brain injury or death at 36 weeks postmenstrual age. The trial finished recruiting 1600 infants in December 2021 and the results are expected this year in 2022 [178]. The neonatal community should strive to obtain the highest level of evidence before incorporating NIRS into clinical practice.

Evidence in micropreemies: The two randomized trials of NIRS oximetry in extremely preterm infants; one in the context of resuscitation after birth [176] and the other in the first three days of life [177] do not provide separate data for micropreemies. At this stage, the recommendation is to await the highest level of evidence before incorporating NIRS into practice.

9.3. Erythropoietin

Erythropoietin, which is used clinically for its erythropoietic effects, is also an important trophic factor in fetal brain development [179]. Erythropoietin has been shown to have neuroprotective effects in pre-clinical models of neonatal brain injury [180]. In addition, results of a meta-analysis of four randomized controlled trials involving a total of 1133 infants showed that fewer infants who received erythropoietin than those who received placebo had a score of less than 70 (which corresponds to standard deviations below the mean) on the Mental Developmental Index of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) (odds ratio, 0.51; 95% confidence interval [CI], 0.31 to 0.81; number needed to treat to prevent a score of <70 in one child 14) [181].

However, a large multicentre, placebo-controlled, randomized trial of erythropoietin in 741 extremely preterm infants (24^{+0} to 27^{+6} weeks of gestation) found no significant difference between groups in the primary outcome of death or severe neurodevelopmental impairment at 2 years of age [182]. In view of limited clinical benefit, early administration of EPO outside of randomized controlled trials (RCTs) is not currently recommended. The results of one ongoing trial NCT02550054 are awaited [183].

Evidence in micropreemies: Around one fourth of the babies included in the large multicentre RCT [182] were born at 24-week gestation. There is insufficient information on the number of babies with birth weight <500 g included in the trial. At this stage, EPO is not recommended in micropreemies outside the context of an RCT.

10. Follow-up and modifying effects of brain injury through early intervention

Early diagnosis of delays in language, cognitive and motor function during the period of neuroplasticity in early life is critical for optimizing long-term outcomes for at-risk infants. Micropreemies should attend long-term neurodevelopmental follow-up in an appropriate service to facilitate early identification of developmental delay(s) and CP, and institution of appropriate early intervention therapies. Early diagnosis of cerebral palsy or high risk of cerebral palsy is now considered standard of care [21], and can be achieved within the first 6 months post-term age [21]. A combination of Prechtl Qualitative Assessment of General Movements and neonatal brain MRI demonstrates greater than 95% accuracy for diagnosis at less than 5 months' corrected age [21]. After 5 months', a combination of neonatal MRI and the Hammersmith Infant Neurological Examination (HINE) shows greater than 90% accuracy for the diagnosis of CP [21]. Early diagnosis using one of these approaches is

recommended wherever possible. Where resources are constrained, the HINE may be utilized in isolation with greater than 90% accuracy for a diagnosis of CP and provides additional information regarding severity of motor impairment [21].

Delays in diagnosis and institution of CP-specific early intervention are associated with reduced long-term function and carer well-being and higher rates of secondary impairments, which are potentially preventable [21]. There are also important neurodevelopmental, psychiatric and health consequences of preterm birth that are felt into adulthood, underscoring the need for extended follow-up across the lifespan [23]. There is clear evidence that early developmental intervention programs for preterm infants positively impact on cognitive and motor outcomes during infancy, with persistence of cognitive benefits to preschool age [22]. Research is ongoing to better define which developmental interventions are most effective. Intensive, task-specific intervention based on environmental enrichment has been shown in a small pilot RCT (the "GAME" trial – Goals – Activity – Motor Enrichment) to result in improved cognitive and motor outcomes for infants at high risk of cerebral palsy [184]. This study is being replicated in a larger population group at present (ACTRN12617000006347) [185]. Similarly, a multisite trial is investigating the effect of two different movement-based therapies for congenital hemiplegia in infants (REACH trial – Randomised Trial of Rehabilitation Very Early in Congenital Hemiplegia – ACTRN12615000190516), the results of which are awaited [186].

Evidence in micropreemies: Early screening for high-risk infants with a combination of Prechtl's general movements assessment, MRI and the HINE is strongly evidence based for the early detection of cerebral palsy [21], including in infants <30 weeks [187]. Assessments as early as 30 weeks' postmenstrual age are being investigated for their predictive value [188]. Although significant heterogeneity exists in gestational ages of preterm infants included in studies of early intervention programs [22], without stratification for extremely preterm infants born at <500 g, one study indicated that infants born at <28 weeks derived a greater benefit from an intervention program than those born at ≥28 weeks [189]. Two additional studies reported no differences in outcomes between infants born at <28 weeks when compared with those born at ≥28 weeks [190,191]. Although further subgroup analysis involving micropreemies is desirable, based on available evidence, including in extremely preterm infants, early intervention for infants at high risk of cerebral palsy should start as soon as possible to optimize neurodevelopmental outcome [21,192,193].

11. Conclusions

Significant improvements in survival amongst extremely preterm infants has shifted focus to further optimizing neurodevelopmental outcomes for this vulnerable patient group. Notable gains have been made in reducing cerebral palsy, however cognitive and motor impairments remain burdensome for many, long after their NICU admission. A number of established, evidence-based neuroprotective strategies exist. Protecting the brain of the micropreemie begins with obstetric and midwifery-led interventions to reduce preterm birth and augment fetal health and wellbeing prior to and at the time of delivery. A shift in approach to supporting cardiorespiratory transition of extremely preterm infants, alongside family-centered, neurodevelopmentally supportive care, recognizes the importance of infant physiology and responses to their environment in modulating brain injury risk. A number of strategies to reduce complications of prematurity associated with brain dysmaturation, such as sepsis, NEC and poor postnatal growth, have become incorporated into modern neonatal intensive care practice. Additional potentially neuroprotective interventions – both in the perinatal period and through early intervention in infancy – continue to be explored. It is hoped that as survival of the smallest, most preterm infants continues to improve, incremental improvements in future quality of life for these children and their families through protection of the vulnerable, developing brain will continue to be possible.

12. Practice points

- Survival without disability for extremely preterm infants continues to improve, however rates of neurodevelopmental impairment remain significant.
- Neuroprotection for micropreemies starts during pregnancy, with strategies to reduce rates of preterm birth and fetal complications that predispose to neonatal brain injury.
- Changes in practice for support of transition to extrauterine life, including respiratory and cord management, are important for ensuring early stabilization and reducing brain injury risk.
- Poor growth, inflammation and ischemia are associated with abnormal white matter development and adverse outcomes. Avoidance of the ischemia and inflammatory cascade associated with sepsis, NEC and prolonged mechanical ventilation, is paramount.
- Attention should be paid to the NICU environment and providing developmentally supportive care, including management of pain, optimizing sleep and facilitating positive parent-infant interactions.
- Neurodevelopmental outcome can be modified by early diagnosis of cerebral palsy and diagnosis-specific early intervention therapies for high-risk infants.

13. Research directions

- Priority should be given to adequately powering clinical trials of neonatal interventions to assess important long-term outcomes, such as neurodevelopment.
- The role of the NICU environment and intensive care provision in modulating brain injury risk, including effects of painful procedures and parent-infant interactions, requires rigorous prospective study.
- Individualized approaches to nutrition and cardiovascular management represent potential opportunities to improve care and should be evaluated further.
- Investigative therapies that are potentially neuroprotective, such as near infra-red spectroscopy (NIRS), erythropoietin and use of stem cells should continue to be explored.

Declaration of competing interest

None.

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