Review Article

Narrative review of perinatal management of extremely preterm infants: what's the evidence?

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Background and Objective: Although significant advances have been made in perinatal medicine during the past few decades, the care of extremely preterm infants remains a great challenge to families, physicians, and the entire health care system. Due to extreme prematurity, extremely preterm infants are at increased risk of mortality and morbidity. The aim of this narrative review is to discuss the perinatal management strategies that may improve the short- and long-term outcomes of these vulnerable infants.

Key Content and Findings: Advances in perinatal care have resulted in increased survival for extremely preterm infants, but these vulnerable infants remain at high risk of mortality and morbidity. Numerous proactive management strategies need to be implemented during perinatal period so that the mortality and impairment rates of extremely preterm infants can be minimized. Some management strategies have been proven beneficial by large meta-analyses or randomized controlled trials. However, the efficacy and safety of some other strategies, especially some emerging strategies, are still unclear.

Conclusions: Many perinatal management strategies have shown to be related to improving outcomes in extremely preterm infants. And a lot of novel strategies are under investigation and some already have promising early results. However, the answers of some important questions in the care of EPIs remain unsatisfying. And the long-term effects of some perinatal strategies are still unclear. Further large-sample, well-designed randomized controlled trials are needed to confirm their safety and efficacy.

Keywords: Extremely preterm; preterm infants; perinatal management; evidence

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Introduction

The World Health Organization (WHO) defines preterm infants as those born alive before 37 completed weeks of gestation. Based on gestational age (GA), preterm infants are further classified into extremely preterm (<28 0/7 weeks), very preterm (<32 0/7 weeks), moderate (32 0/7–33 6/7 weeks) and late preterm (34 0/7–36 6/7weeks) infants (1). In the past few decades, preterm birth rates have risen in most countries. The global premature birth rate was estimated to be 9.8% in 2000, 11.1% in 2010, 10.6% in 2014, and extremely preterm births accounted for about 5% in all preterm births (2,3). In China, the incidence of preterm birth has also been steadily increasing from 5.36% in 1990–1994 to 7.04% in 2016 (4), and the proportion of [extremely preterm infants (EPIs)] is 1.1% in alive born infants (5). These figures are likely to increase in the future due to an increase in maternal age and use of assisted conception.

Table 1 The search strategy summary

Items	Specification
Date of search	From February 12, 2021 to February 22, 2021
Databases and other sources searched	PubMed, Web of Science, Cochrane Library, OVID and Embase
Search terms used	Infant, extremely premature; infant, premature; infant, newborn; obstetric labor, premature/prevention and control; premature birth/prevention and control; infant, premature, diseases/nursing; infant, premature, diseases/prevention and control; infant, premature, diseases/therapy; perinatal care; intensive care, neonatal; peripartum period/drug effects; perinatal management; perinatal care; extremely preterm; extremely preterm infant; extremely premature infant; EPI; small for gestational age infant; low birth weight infant; therapy; treatment; protection; management; strategy.
Timeframe	From January 01, 2011 to February 22, 2021
Inclusion criteria	Study type: clinical trial, randomized controlled trial, review, systematic review and meta-analysis. Language restrictions: English
Selection process	All the authors conducted the selection after discussion. The title and abstract of each article were screened for the selection of relevant articles

EPI, extremely preterm infant.

Studies from different regions and healthcare facilities suggest that the survival rate has increased in EPIs during the past few decades (6-10). However, studies of neurodevelopmental outcomes among EPIs have shown mixed results (11-13). And there is concern that declining mortality in EPIs may lead to a larger number of infants surviving with morbidity, especially neurodevelopmental impairment. In China, the rate of survival for infants born at 24–27 weeks increased from 56.4% in 2010 to 68.0% in 2019, but the rate of major morbidities, i.e., bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), white matter injury (WMI), neonatal necrotizing enterocolitis (NEC), sepsis, or severe retinopathy of prematurity (ROP), also increased from 52.0% in 2010 to 82.3% in 2019 (10). Therefore, despite improvements over time, the rates of short- and long-term adverse outcomes remain high in EPIs. For this reason, we collated a variety of perinatal interventions for EPIs, which were recommended by guidelines or supported by large meta-analyses or randomized controlled trial (RCTs). We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-51/rc).

Methods

Literature searches were conducted in PubMed, Cochrane Library, OVID, Embase, and Web of Science, specifically for studies related to perinatal management of EPIs from 2000 to 2021 (*Table 1*). Our searches were limited to English language publications. Observational studies, RCTs, systematic reviews and meta-analyses were included. The title and abstract of each article were screened for the selection of relevant articles.

Antenatal management of EPIs

Antenatal counseling

Due to the uncertainty in diagnosis and prognosis, the management of extremely preterm birth can be very challenging for both physicians and family members. The primary goal of antenatal counseling is to support the family to make informed decisions about interventions to be implemented. Various information (e.g., risk assessment, mortality and morbidity figure, ongoing support, burden of hospitalization) should be included in an effective antenatal counseling (14). Although antenatal counseling can be guided by general recommendations (15,16), it should be individualized in clinical practice because each situation is unique. Ideally, antenatal counseling is well informed, ethically sound, consistent within medical teams, and accordant with the family's wishes.

Furthermore, the family should be involved in the

management planning and relative decision-making for extremely preterm birth whenever possible. The preferred mode of decision-making is shared decision-making which combines the points of view from both physicians and family members (17). The British Association of Perinatal Medicine Framework working group published in 2019 outlined an approach to assist in decision-making and management planning of extremely preterm birth (18).

Antenatal transfer

Studies from different regions have reported better outcomes of EPIs born in tertiary obstetric centers with neonatal intensive care units (NICUs) than those born in non-tertiary facilities without NICUs (19-21), especially in tertiary centers with a lot of EPIs, because these tertiary centers can usually provide more comprehensive maternal and infant care.

When the woman with a high risk of extremely preterm labor presents at a non-tertiary facility, she can be transferred to a tertiary obstetric center with NICU before delivery (antenatal transfer), or the newborn can be transferred after stabilization in the non-tertiary facility (postnatal transfer). Current studies suggest that infants transferred to tertiary centers after birth might have worse outcomes than those born at tertiary centers, including higher rates of mortality and severe brain injuries (22-24). Many national guidelines also agree antenatal transfer is a better selection (18,25), which could avoid the risk of delivery in non-tertiary facilities, improve neonatal outcomes, and reduce mother-infant separation. However, often women presenting in threatened extremely preterm labor do not deliver in the subsequent 24 hours (18). There are several forecasting strategies, but only fetal fibronectin test and cervical length measurement have showed high predictive performance (26,27). Mothers who are medically unstable (e.g., placental abruption or eclampsia) or present in advanced preterm labor are not suitable for ambulance travel due to the risk of suboptimal clinical monitoring during transfer (28) or the risk of birth in transit (18). In addition, antenatal transfer may pose challenges for the family as well as obstetric and ambulance services. A decision for antenatal transfer should include documented discussion with the family and the receiving tertiary center to ensure the balance benefits and risks of the mother and infant.

Antenatal corticosteroids

Administering antenatal corticosteroids (ACS) to women anticipated preterm birth is one of the most important antenatal managements available to improve newborn outcomes. Current guidelines recommend ACS administration to women at high risk of preterm birth from 23 to 35 weeks (15,16,29).

A recent large prospective cohort study including 117,941 neonates revealed that ACS group was associated with lower mortality and morbidity among infants born from 23 to 34 weeks' gestation in compared with control group (30). In addition, ACS administration seems to present a greater reduction on mortality in infants born at the lowest gestations (31). The most recent Cochrane review has shown that single course of ACS reduced a range of adverse outcomes to preterm in infants born at 24–34 weeks gestation, including perinatal mortality, neonatal mortality, respiratory distress syndrome (RDS), IVH, systemic infections, NEC and developmental delay in childhood (30).

Betamethasone and dexamethasone, two commonly used corticosteroids, have similar efficacy and safety profiles (32,33). While WHO supports the use of dexamethasone, which is cost-effective and widely available (34), choice of ACS use can base on provider preference, cost, and availability. The recommended treatment option is a single course of two 12 mg doses of a 1:1 mixture of betamethasone phosphate and betamethasone acetate given at 24-hour intervals or four 6 mg doses of dexamethasone phosphate separated by 12 hours (35). Although repeated doses may lower the risk of neonatal severe lung disease, there were insufficient data to exclude other beneficial or harmful effects (36).

For the optimal use of ACS in different medical and social-economical settings, more information remains required in several important areas. Two large RCTs assessing the efficacy of ACS in low- and middle-income countries, the WHO ACTION-I trial (37) and ACT trial (38), came to different conclusions, which suggests that the results of efficacy trials conducted in high-income countries may not be applicable to low-resource settings. Furthermore, strategies to promote ACS use may increase the risk of unnecessary ACS exposure to women in whom ACS is not indicated (39). Additionally, there is limited evidence regarding the risks and benefits of ACS in

multiple pregnancies and other high-risk obstetric groups. The optimal dose and dose interval are still debated. Individualized ACS therapy may be of great potential in the future.

Magnesium sulfate

Magnesium sulfate ($MgSO_4$) has been widely used for prophylaxis and treatment of preeclampsia in obstetrics (40). Currently, $MgSO_4$ is emerging as a neuroprotective agent in preterm births and many professional guidelines recommend the use of antenatal $MgSO_4$ for neuroprotection in women prior to anticipated preterm birth (41-43).

Multiple clinical trials have demonstrated the effect of antenatal $MgSO_4$ in the reduction of severe and moderate cerebral palsy (CP) (44-47). Interestingly, a recent meta-analysis has shown that antenatal $MgSO_4$ decrease the incidences of severe IVH, the need for intubation and/or chest compressions in the delivery room, although the effects are only borderline-significant (48). Several studies reported that antenatal $MgSO_4$ increased the risk of spontaneous intestinal perforation, NEC and mortality in EPIs (49,50). However, the incidences of these complications were significantly increased when $MgSO_4$ was used at higher doses than the recommended (loading dose 4 grams, 1 gram per hour as maintenance dose). It is unknown whether a loading dose of 4 or 6 grams alone is sufficient and whether the course should be repeated 24 hours after the initial loading dose if the woman is still at high risk of delivering preterm. The current standardized protocol is used in all patients without adjusting maternal or fetal factors that may affect serum magnesium levels. The specific adverse neonatal outcomes in particular obstetric groups are also unclear. Follow-up studies found no evidence of harm in school-age children who were exposed to $MgSO_4$ prenatally (51,52).

Tocolysis

There are various kinds of tocolytics available, including β adrenoceptor agonists, cyclooxygenase inhibitors, magnesium sulfate, calcium-channel blockers and oxytocin receptor antagonists (53,54). Due to side effects, β adrenoceptor agonists and cyclooxygenase inhibitors are mainly used for second-choice tocolytics. Although $MgSO_4$ is neuroprotective, it may be ineffective as a tocolytic agent (55). Therefore, calcium-channel blocker nifedipine and oxytocin inhibitor atosiban are the two most frequently used tocolytics. Their efficacy and safety were compared in APOSTEL III trial. The perinatal outcomes were comparable between two groups, but a non-significant increase in mortality was found in the nifedipine group (56). And in the subsequent long-term follow-up study, there was no significant difference between nifedipine and atosiban (57).

The choice of the most appropriate tocolytic agent will be a balance of efficacy, safety, and cost. APOSTEL 8 study is ongoing to test the hypothesis that atosiban is effective, safe and cost-effective in late preterm birth (30–34 weeks) when compared with placebo (58). However, there is insufficient evidence about tocolytics for women with the risk of extremely preterm labor. In a meta-analysis, no apparent effectiveness was found for tocolytics to delay delivery for women with extremely preterm condition, but the evidence was rated to be very low quality (59).

Postnatal management of EPIs

Delivery room management

Delayed cord clamping (DCC) and umbilical cord milking (UCM)

DCC is an effective method of increasing cardiac output, enhancing arterial oxygen content, and improving oxygen delivery in preterm infants.

Most professional organizations now recommend DCC for 30–60 s in preterm infants (60-62). Meta-analyses identified that DCC reduced neonatal mortality by 30%, any IVH, need for blood transfusion, and NEC in EPIs (63-65). Although DCC may slightly increase the risk of polycythemia and jaundice, it is not associated with morbidity (64). DCC is generally not provided to infants who need immediate resuscitation, but a recent RCT showed that providing resuscitation with an intact cord might improve EPIs' outcomes at discharge when compared to early cord clamping. Large multicenter trials are urgently needed (66) to confirm the findings from the studies with a small sample size and wide confidence intervals.

UCM is a more rapid approach to enhance placental transfusion, which can be done within 20–30 seconds and is independent of uterine contraction. This technique requires grasping the unclamped umbilical and stripping the blood from the placental to the fetal side four times. For newborns considered too unstable to wait 30–60 seconds for DDC, UCM may be more advantageous than DCC (67). For cord milking versus early cord clamping, there were insufficient

data to make clear comparisons on outcomes (63), except that UCM may increase the risk of severe IVH in infants born at less than 28 weeks gestation (68).

Supplemental oxygen

Owing to reduced antioxidant defense and frequent exposure to oxygen during stabilization in the delivery room, Preterm newborns are particularly vulnerable to oxidative stress (69). Many complications of prematurity, such as ROP, BPD, IVH and periventricular leukomalacia (PVL), appear to be related with oxygen toxicity (70).

The 2019 International Liaison Committee on Resuscitation suggested starting with a lower oxygen concentration (21–30%) in the resuscitation of preterm infants, but they also acknowledged the need for further evidence (71). For meta-analysis of EPIs receiving respiratory support at birth, there was no statistically significant benefit or harm between lower initial FiO_2 (≤0.30) and higher initial FiO_2 (≥0.6) for the following outcomes: BPD, IVH, ROP, patent ductus arteriosus (PDA), NEC and overall mortality (72). However, an un-prespecified analysis demonstrated that using room air to initiate resuscitation was associated with a higher risk of death than 100% O_2 among infants <28 weeks' gestation (73). The results of this study should be interpreted with caution due to its small sample size and early termination. Similarly, the subject of optimal oxygen saturation (SpO_2) ranges has been debated for several decades. Recent meta-analyses showed that targeting lower (85% to 89%) SpO_2 compared to higher (91% to 95%) SpO_2 had no significant effect on the primary composite outcome of death or major disability at a corrected age of 18 to 24 months (74,75). The lower SpO_2 target range was associated with a higher risk of death and NEC but a lower risk of ROP treatment (74). However, more information regarding the safest and most effective use of supplemental oxygen to minimize mortality and morbidity in preterm infants remains needed.

Respiratory management

Respiratory support

Successful transition from fetal to postnatal life requires the opening and aeration of the lung. Due to weak respiratory drive, immature lung structure, surfactant deficiency and compliant chest wall, this process is impaired in many EPIs (76). Consequently, the majority of them require respiratory support after birth to ensure adequate gas exchange. However, invasive mechanical ventilation (IMV) is an important risk factor of BPD, which remains one of the major morbidities in EPIs and is associated with many respiratory and neurological adverse outcomes (77). Non-invasive respiratory support, such as nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV), has been shown to decrease the risk of lung injury and BPD in comparison with IMV (78).

Use of nasal continuous positive airway pressure (NCPAP) immediately after birth can facilitate lung recruitment and reduce lung injury by avoiding mechanical ventilation related baro-volu-trauma or atelecto-trauma from repeated collapse and expansion of the alveoli during room air breathing (79). NCPAP can also help to establish and maintain a functional residual capacity (FRC). Several large RCTs compared early NCPAP with routine intubation and surfactant administration as an initial strategy in the delivery room (80-83). In meta-analyses of these RCTs, NCPAP reduced the need for mechanical ventilation and the incidence of death or BPD, without increasing risk for pneumothorax or other adverse events (84-86). Based on these findings, many neonatal resuscitation guidelines recommend the use of NCPAP as a mode of ventilator support for preterm babies soon after birth (87). However, a long-term follow-up study found that there was no significant improvement in BPD or impaired lung function in EPIs at eight years of age with the use of NCPAP (88). The exact reason for the lack of long-term benefits with NCPAP is unclear. Further, NCPAP has a high failure rate, with about 43% of infants commencing on NCPAP at 25–28 weeks' gestation needing endotracheal intubation subsequently (89). An ongoing multicenter RCT is conducted to evaluate the optimum positive end expiratory pressure (PEEP) needed to prevent NCPAP failure in preterm infants (90).

NIPPV is a pressure-controlled, time-cycled mode of ventilation. It mimics endotracheal ventilation, but the pressures are delivered through nares (91). A Cochrane meta-analysis comparing early NIPPV to early NCPAP indicated that NIPPV decreased respiratory failure, need for intubation, and extubation failure in preterm infants, but there was no significant difference in the outcome of BPD between the two groups (92). Another Cochrane meta-analysis comparing NIPPV to NCPAP for respiratory support post-extubation founded a significant reduction in extubation failure and the need for re-intubation in the NIPPV group. Still, there was no significant difference in the rate of BPD between the two groups (93). A very recent

sub-analysis showed that the failure of primary noninvasive respiratory support was not decreased by NIPPV in extremely low birth weight infants (94). Thus, it is not clear whether NIPPV is superior to NCPAP to prevent noninvasive respiratory support failure in EPIs.

Synchronized NIPPV (SNIPPV) means the use of NIPPV with synchronization to the patient's inspiratory efforts. SNIPPV was shown to be more effective than NIPPV and NCPAP to reduce intubation among preterm infants with respiratory failure, improve the success of extubation, and treat apnea of prematurity (AOP), without detected adverse effects (95). Although a meta-analysis comparing different non-invasive modes revealed that SNIPPV was associated with decreased BPD compared to other modes (96), no large scale RCTs has shown a definite benefit with the use of SNIPPV to decrease BPD in compared with other modes until now. Additionally, SNIPPV is more expensive and less popularized.

Sustained inflation (SI) was regarded as an alternative to NIPPV in the resuscitation of neonates at birth. Recently, the largest RCT conducted to assess the safety and efficacy of SI in EPIs (the SAIL trial), was stopped early because of higher mortality within the first 48 hours of life in SI group. Of note, it has shown that a ventilation strategy involving two sustained inflations did not reduce the risk of BPD or death at 36 weeks' postmenstrual age than standard intermittent positive pressure ventilation (97). For that reason, sustained inflations may not be suitable for EPIs.

Pulmonary surfactant (PS)

PS plays an important role in the management of RDS (98). Traditionally, surfactant is delivered via an endotracheal tube and in conjunction with mechanical ventilation. However, negative consequences of mechanical ventilation, such as pneumothorax and BPD, are well known. The first effort to minimize exposure to mechanical ventilation during surfactant delivery is INtubation-SURfactant-Extubation (INSURE) technique, which is widely accepted in clinical practice now (99,100). To further preventing intubation in surfactant delivery, newer strategies of less invasive surfactant administration (LISA) are being investigated, including thin catheter administration, pharyngeal administration, laryngeal mask airway, and aerosolized surfactant administration (101). Of these strategies, thin catheter administration, often referred to surfactant administration through a thin tracheal catheter in spontaneously breathing infants, is the most studied.

A large cohort study conducted by the German Neonatal Network reported that LISA reduced the incidence of mortality, BPD, IVH grade II-IV, and ROP in infants ≤28 weeks of GA compared with surfactant delivery via endotracheal intubation (102). However, an increased risk for focal intestinal perforation was observed in infants <26 weeks of GA with the use of LISA (102). Several studies have compared LISA to INSURE, and found improvement in BPD and mechanical ventilation requirement was inconsistent between studies (103-107). Meta-analyses indicated that LISA is superior to CPAP alone or the INSURE technique in the reduction of BPD and death (108-110). However, these findings are limited by the overall low quality of evidence and lack of robustness in higher-quality trials.

There are two commonly used animal-derived surfactants: porcine mined surfactant and bovine mined surfactant. In a meta-analysis, treatment with porcine surfactant is likely to decrease the risk of neonatal mortality, BPD, and other adverse outcomes, when compared to bovine mined PS (111). Nevertheless, subgroup analysis indicated that the reduction in morbidity and mortality risk was limited to the trials using higher initial doses of porcine mined lung surfactant (111). It is uncertain whether the differences are from compositional differences and/or doses. The licensed dose of PS for preterm infants with RDS is 100–200 mg/kg. A higher dose of surfactant (200 mg/kg) may reduce the need for invasive ventilation and retreatment, as well as indicating the possibility of reduced mortality and oxygen requirement at 36 weeks' postmenstrual gestation (111,112).

Caffeine

AOP is a common complication in preterm infants. Due to the immaturity of the brainstem and peripheral chemoreceptors, almost all EPIs exhibit symptoms of apnea, bradycardia and desaturation, which may cause damage to the developing brain and other organs (113). Methylxanthine has been routinely used to treat AOP for more than 40 years. Caffeine, a methylxanthine derivative, is the initial drug of choice among all the methylxanthines due to its efficacy, better tolerability, wider therapeutic margin, and longer half-life (114). In addition, the Caffeine for Apnea of Prematurity (CAP) trial revealed many other benefits of caffeine therapy for very low birth weight infants, including reductions in the incidence of BPD, duration of mechanical ventilation, need for PDA treatment, the severity of ROP, and improved long-term neurodevelopment related to motor function and enhanced

lung function (115-118).

Although several national guidelines suggest that earlier caffeine treatment is associated with increased benefits, none of them has specified the exact timing of therapy (119). A post-hoc subgroup analysis of results from CAP trial identified a greater reduction in the need for ventilation with earlier initiation of caffeine (within the first 3 days of life) (120). More recently, a meta-analysis including 6 cohort studies and 8 RCTs suggests that early caffeine (within the first 3 days of life) therapy reduced the incidence of BPD and may help to decrease the burden of morbidities in preterm infants (121). However, these findings need to be interpreted with caution because the evidence is generally of low quality. Most cohort studies had inherent methodological problems and small sample sizes of the RCTs.

There is also no consensus on the optimal dose of caffeine therapy. Meta-analysis comparing high (loading dose >20 mg/kg/day, maintenance dose >10 mg/kg/day) versus low (loading dose ≤20 mg/kg/day, maintenance dose ≤10 mg/kg/day) dose of caffeine demonstrated a decreased rate of extubation failure, apnea, BPD, and a shorter duration of mechanical ventilation in the high dose group, with no impact on mortality (122). Furthermore, a recent retrospective study reported an association between a higher average daily dose of caffeine and improved neurodevelopmental outcomes (123). However, some concerns about adverse effects have limited the use of high-dose caffeine, including tachycardia, cerebellar hemorrhage, and seizure (124-126). Further studies, specifically well-designed RCTs, are needed to determine the optimum timing and dose for caffeine administration in neonatal care.

Postnatal corticosteroids

Inflammation plays a key role in the pathogenesis of BPD. For this reason, postnatal corticosteroids are regarded as a therapeutic option for BPD due to their anti-inflammatory characteristics (127). Many studies have suggested that postnatal corticosteroids have considerable short-term benefits on lung function in infants with BPD. However, there is increasing concern that the benefits of postnatal corticosteroids, especially dexamethasone, may not outweigh the short- and long-term complications, including gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension and adverse neurodevelopmental outcomes (128,129).

In the PREMILOC trial, early systemic low-dose hydrocortisone (1 mg/kg/day for the first 7 postnatal days, 0.5 mg/kg/day for another 3 days) was found to be associated with a significantly increased survival without BPD in EPIs, and no significant short-term adverse effects was found, except a higher rate of sepsis in infants born at 24 to 25 weeks of gestation when compared with placebo (130). There was also no significant difference in neurodevelopmental outcomes at 2 years of age between the two groups (131). In addition, a more recent secondary analysis of PREMILOC trial even reported a statistically significant improvement in neurodevelopment in infants born at 24 to 25 weeks GA with the use of early low-dose hydrocortisone (132). While, another large RCT (STOP-BPD study) suggested that late systemic hydrocortisone (initiated between 7 and 14 days after birth, a 22-day course with cumulative dose of 72.5 mg/kg) did not improve the composite outcome of death or BPD, and a higher rate of hyperglycemia requiring insulin therapy was reported in hydrocortisone group (133). Hence, further studies focusing the timing, dosage and duration of postnatal hydrocortisone treatment are needed.

Inhaled and intratracheal administered corticosteroids are becoming increasingly attractive, which may reduce lung inflammation with fewer side effects (134). The Cochrane review comparing inhaled corticosteroids with systemic corticosteroids reported similar effectiveness and safety profiles in the treatment of BPD, but the neurodevelopmental outcomes of inhaled corticosteroids remain uncertain (135). As for the intratracheal administered corticosteroids, a recent RCT showed that intratracheal administration of budesonide with surfactant significantly reduced the incidence of BPD or death in VLBW infants with RDS when compared to surfactant alone, without significant difference in short-term outcomes or long-term complications at a mean age of 30 months (136). Further large-sample, double-blind trials are still needed to confirm its safety and effectiveness.

Circulatory management

PDA closure

The incidence of PDA is inversely related to GA. On day four after birth, the ductus arteriosus remains patent in about 10% of preterm infants born at 30–37 weeks gestation, 80% of those born at 25–28 weeks, and 90% of those born at 24 weeks. On day seven after birth, these rates decline to approximately 2%, 65%, and 87%, respectively (137). PDA and resulting left-to-right ductal shunt can increase pulmonary blood flow and decrease systematic perfusion,

which might be associated with multiple morbidities, including IVH, pulmonary hemorrhage, BPD, NEC, and abnormalities of cerebral perfusion (138,139). However, there is still a lack of evidence to determine whether the PDA or simply the result of prematurity caused these complications. Consequently, the optimal management of PDA is widely debated (140,141).

COX inhibitors, such as indomethacin or ibuprofen, are the mainstays of pharmacologic treatment. Ibuprofen appears to be as effective as indomethacin in the closure of PDA, but oral ibuprofen offers a lower risk of NEC and transient renal insufficiency (142). The standard dosing of ibuprofen is 10 mg/kg for the first dose and half (5 mg/kg) for the second and third doses in 24 hours. In a network meta-analysis, a high dose of oral ibuprofen was found to be more effective in hemodynamically significant PDA (hs-PDA) closure than standard doses of intravenous ibuprofen or indomethacin (143), while there is a lack of evidence regarding long-term outcomes of using ibuprofen and indomethacin. Paracetamol does not appear to be as effective as indomethacin or ibuprofen in preterm infants, but it is an attractive option when COX inhibitors are contraindicated or ineffective (144).

Two Cochrane reviews demonstrated that prophylactic indomethacin and ibuprofen reduced the incidence of symptomatic PDA, the rate of severe IVH and the need for surgical ductal closure, but with no evidence of making a difference in mortality, BPD, NEC or neurodevelopment (145,146). Indomethacin was usually considered the preference for the prophylaxis of PDA because ibuprofen may be less efficient in the reduction of severe IVH (145), however, there is no high-quality RCT directly comparing the prophylactic and long-term effects of ibuprofen and indomethacin on PDA. Furthermore, prophylactic treatment may cause the overtreatment of infants with PDA that will never be hemodynamically significant.

Transcatheter PDA closure (TCPC) has become feasible in infants less than 1.5 kg (147). Compared with pharmacologic treatment that requires a long period to work and is not 100% effective, TCPC can close the PDA more immediately and definitely. Compared with surgical ligation, there is no need to cut and suture the infant's chest and to handle the premature lung; thus the risk of postoperative is lower (148). Recent meta-analysis showed the technical success of TCPC was 92.2%, overall adverse events and clinically significant adverse events incidence was 23.3% and 10.1%, respectively, but significant heterogeneity and publication bias were observed (149). Therefore, TCPC represents a potentially attractive alternative, especially when pharmacologic treatment has failed. Large, pragmatic, multicenter studies that systematically evaluate TCPC are still needed.

Recently published trials have shown the feasibility and efficacy of conservative approaches in PDA management. The PDA-TOLERATE Trial suggested that a conservative approach had similar PDA ligations and similar secondary outcomes when compared with early routine treatment in EPIs (150). Another RCT also showed that conservative nonintervention approach was noninferiority when compared with oral ibuprofen in the closure of hs-PDA and reduction of BPD or death (151). Nevertheless, in some cases, conservative management may result in low success rate and increased complications of PDA. Further investigations are needed to determine which infants are most likely to benefit from active or conservative PDA management strategy.

Blood pressure management

The hemodynamic status in EPIs can be disrupted due to multiple factors, including physiological fetal shunts, pathological conditions, and iatrogenic effects of ongoing treatments (152). Blood pressure (BP) is routinely measured as a proxy for the estimation of infants' hemodynamic status. However, defining the hypotension or hypertension in newborns is challenging because blood pressure varies with the GA, post-menstrual age and body weight (153,154). A mean blood pressure (measured in mmHg) lower than the infant's GA is the most frequently used criteria for neonatal hypotension (155). While neonatal hypertension is diagnosed when the BP values measured on 3 separate occasions are over the 95th percentile for the infant's post-menstrual age. And BP values over the 99th percentile persistently are defined as severe neonatal hypertension (156).

Rates of hypotension have been reported to be 15–50% in studies of EPIs (157-159). However, the management of hypotension is widely debated. Volume expansion followed by an infusion of dopamine is the most frequently used treatment for hypotension, but its benefits and safety profiles remain unclear. Observational studies suggested that inotropic treatment in hypotension was associated with a higher rate of IVH (160) and an increased risk of death or neurodevelopmental impairment/developmental delay (161). Conversely, in the EPIPAGE 2 French national cohort study, antihypotension treated group had a significantly increased survival rate without short-term adverse events (162). The HIP trial, a multicenter RCT

designed to compare restrictive inotrope treatment with standard treatment, terminated early due to significant enrolment issues (7.7% of planned recruitment) (163). Currently, many physicians think that an abnormal BP value itself may not be a factor needing urgent intervention before signs of poor perfusion occur. Biochemical indexes, functional echocardiography and near-infrared spectroscopy can also play a role in the assessment of hemodynamic status. Besides, although dopamine is the most commonly used antihypotensive agent, dobutamine, epinephrine, corticosteroids, milrinone, and vasopressin have also been used for the treatment of neonatal hypotension (152). Well-designed RCTs are strongly needed to determine the optimal antihypotensive medication, as well as the most appropriate treatment timing and dose.

Hypertension occurs in up to 3% of infants admitted to NICU, but the exact prevalence of hypertension in preterm infants has not been determined (164). Furthermore, no studies exist on the long-term outcomes of preterm infants with short- or long-term hypertension, and there is little evidence about the management of neonatal hypertension. In such circumstances, clinical expertise may be needed to guide decision-making. And the treatment of neonatal hypertension should consist of treating the correctable causes, such as inotropes, steroids, endocrinal disorders, and excessive fluids intake (165). Various antihypertensive agents have been utilized in preterm infants with hypertension, including calcium channel blockers, vasodilators, angiotensin converting enzyme inhibitors, α-adrenergic antagonist, α and β adrenergic antagonist, and diuretics, but almost none of them have been systematically studied in EPIs (166).

Infection management

Despite consistent advances in care practices, neonatal sepsis remains an important cause of morbidity and mortality in premature infants (167-169). The risk of infection in EPIs is particularly high due to immature immune system, prolonged hospital stay, frequent invasive procedures (e.g., endotracheal intubation and intravascular catheterization) and a lack of full enteral feeding (170). According to the age of onset and timing of the sepsis episode, neonatal sepsis can be classified as early (EOS) and late (LOS) onset sepsis (171). Usually, the cut-off point between EOS and LOS is 72 hours.

Clinically, the encountered initial signs of neonatal sepsis are variable and often very subtle, but the time from subtle signs to multisystem organ failure and meningitis can be only several hours. The most common early symptoms are temperature instability (high or low), tachypnea, lethargy, and poor feeding (172). The most important diagnostic testing is a blood culture drawn before antibiotics administration (172). As one of the most extensively studied inflammatory markers, Serial C reactive protein (CRP) measurement is available to detect asymptomatic slow-onset infections, exclude possible infections, and monitor infants' response to the anti-infective treatment. CRP may be unreliable for early diagnosis of neonatal sepsis because it takes about 10 to 12 hours to elevate and 36 to 48 hours to reach the maximum level. Moreover, CRP may spuriously increase in some non-infectious conditions, such as meconium aspiration and fetal distress (173). Another extensively studied biomarker, procalcitonin (PCT), is slightly more sensitive and specific than CRP. Nevertheless, PCT was also shown to be increased by many non-infectious perinatal conditions (174). Hence, CRP, PCT and other potential biomarkers all need to be studied further to improve their diagnostic accuracy.

Empiric treatment with broad-spectrum antibiotics is still the main treatment of neonatal sepsis. Once the pathogen and its antibiotic sensitivity are characterized, the use of antibiotics should be narrowed. Prophylactic maternal antibiotics following preterm prelabor rupture of membranes (PPROM) is recommended, which is related to prolongation of pregnancy and improvements in short-term neonatal outcomes (175,176). Furthermore, various strategies have been implemented in NICUs to decrease the incidence of infection, including attention to hand hygiene, improved central line care with central line bundles, less-invasive assisted ventilation, and antimicrobial prophylaxis (168,177). Meanwhile, with the extensive use of antibiotics, the emergence of multi-drug resistant organisms is also increasingly reported in NICUs worldwide (178). Observational studies have found an association between antibiotic overuse and increased rates of complications in EPIs, including BPD, NEC, fungal infection and even death (179-182). To address these challenges, neonatal providers developed antibiotic stewardship, a coherent set of actions aimed at optimizing antibiotic use to prevent the emergence of resistant species and protect infants from the side effects of unnecessary medication, such as reducing the use of broad-spectrum antibiotics and initial empiric antibiotics (183). A recent retrospective study confirmed the feasibility of antimicrobial stewardship interventions in EPIs In

this study, following the implementation of a limited antimicrobial stewardship intervention, a significant reduction of antibiotic treatment days was achieved without increased adverse outcomes in EPIs (184).

Nutritional management

Parenteral to enteral nutrition

The ultimate goal of nutritional management is to ensure a growth rate close to intrauterine growth and optimize neurodevelopmental outcomes. In EPIs, complete parenteral nutrition should be applied shortly after birth to avoid a catabolic state since the newborn infant's own caloric reserves and enteral intake are limited (185). Because of immaturity and growth needs, EPIs have a very high demand for energy. The resting metabolic rate is around 40 kcal/kg/d in a thermo-neutral environment when the infants are on complete parenteral nutrition. Glucose, protein, lipids should provide 30–35%, 10–15%, 25–40% of daily energy intake, respectively (186). Although early amino acid and energy intake is crucial to promote extrauterine growth, high-dose amino acid (3.6 g/kg/d) nutrition may be harmful due to the metabolic consequences (187). Further, the role of some nonessential amino acids, such as cysteine, glutamine, and arginine, has not been confirmed yet. An adequate amount of other nutrients, such as vitamins and minerals, is equally important as the inadequacy of these nutrients may also result in short- and long-term adverse outcomes (188).

The transition from parenteral nutrition to enteral nutrition is the next challenge. It commonly starts with 3- to 5-day course of trophic feeding (≤24 mL/kg/d) after birth, then transfers to progressive feeding (increments of feeding volumes by 20–24 mL/kg/d) until full enteral feeding (≥120 mL/kg/d) is achieved (189). Recently, increasing evidence is available to support early total enteral feeding in EPIs. A retrospective study involving 192 EPIs identified that short duration (3 days or less) of trophic feeding was associated with early initiation of full enteral feeding, without a higher risk of NEC or death (189). More recently, a single-center RCT compared early progressive feeding without trophic feeding to delayed progressive feeding after a 4-d course of trophic feeding. The results indicated that early progressive feeding increased the duration of total enteral feeding days, reduced the use of parenteral nutrition and the need for central venous access without increasing the risk of postnatal growth restriction at 36 weeks of postmenstrual age (190).

Breast milk and nutrient fortifiers

Breast milk is the preferred source of nutrition to EPIs not only for its nutritional value but also for its immune protection and for its role in modulating the gut microbiota, which plays an important role in intestinal maturation (191). A recent meta-analysis comparing breast milk with preterm formula showed that breast milk significantly reduced the incidence of NEC in EPIs, and the higher the dose, the greater the protective effect. Breast milk also provided a possible reduction in LOS and severe ROP. However, there is insufficient evidence to draw any conclusions regarding the role of breast milk on BPD or neurodevelopment (192).

Since mothers' own milk or donor breast milk alone cannot meet the increased energy and protein demands of preterm infants, supplementation with multi-nutrient fortifiers is required (193). Two kinds of nutrient fortifiers are commonly used to augment the nutritional content of breast milk: bovine milk-derived fortifier and human milk-derived fortifier. Low-certainty evidence suggested that human milk-derived fortifier may not improve growth or alter the risk of NEC, feeding intolerance, infection, and mortality compared to bovine milk-derived fortifier (194). Presently, multiple-strain probiotics have also been introduced into a clinical routine in some countries (195).

Neurological management

Erythropoietin

Although survival rates for EPIs are increasing steadily, the percentage of EPIs survived with neurodevelopmental impairment has not changed significantly (13). One or more major impairments (e.g., CP, intellectual disability, deafness, or blindness) may develop in about 40% of EPIs (13). In addition, a high prevalence of behavioral, social and emotional problems continues to dominate the literature relating to EPIs' childhood outcomes and these problems can persist into adult life (196). Among the candidate agents to prevent brain injury or improve development, erythropoietin (EPO) has been the most promising and studied (197). EPO's neuroprotective mechanisms may include anti-apoptotic, anti-inflammatory, neurotrophic, and anti-oxidant effects thus promoting angiogenesis, neurogenesis and oligodendrogenesis in the brain (198).

A recent Cochrane review identified that early EPO therapy significantly reduced the incidence of IVH, PVL, and NEC, without significant difference in the risk of severe ROP (grade ≥3) or mortality, whereas the neurodevelopmental outcomes at 18 to 22 months and

later varied in published studies (199). Another meta-analysis of 4 RCTs involving a total of 1133 very preterm infants showed that prophylactic EPO administration decreased the rate of severely impaired neurodevelopmental scores (Bayley Scores of Mental Development Index <70) at a corrected age of 18 to 24 months, without affecting other neurodevelopmental outcomes (200). In contrast, a multicenter, double blind, randomized trial (PENUT trial) involving 741 infants founded that high-dose erythropoietin did not significantly change neurodevelopmental impairment or death in very preterm infants at two years of age (201). A smaller trial also reported similar negative findings for erythropoietin at two years and five years of age (202,203). Notably, an observational study revealed that EPIs treated with erythropoietin had meaningfully better neurodevelopmental outcomes at six to seven and ten to thirteen years of age compared with untreated infants (204). Therefore, an age of two or five years may be too early to show benefits; the protective effects of erythropoietin on the survival of brain cell population and the formation of neural network are more related to reaching the later milestones. It is also possible that the different dosing regimens and durations of treatment have contributed to the absence of neuroprotection, which highlights the importance of exploring the optimal dose and duration of erythropoietin therapy.

Other potential neuroprotective therapies

Melatonin, vitamin D, and stem cell therapy have all shown neuroprotective potential in various studies, and researches are evaluating these and other interventions. Melatonin combined with therapeutic hypothermia may reduce seizures and white matter abnormalities at 2 weeks of age and improve survival without neurological abnormalities at 6 months of age, according to a small RCT of full-term neonates with HIE (205). No long-term follow-up study has been reported. A multicenter RCT is ongoing to address the role of melatonin in newborns with a GA of less than 29^{+6} weeks.

Vitamin D plays an important role in brain development. In preclinical models of brain injury, Vitamin D has demonstrated a range of neuroprotective effects, such as immunomodulatory and anti-inflammatory effects (206). Although there is no sufficient clinical evidence that vitamin D supplementation is neuroprotective for preterm infants, maternal vitamin D deficiency appears to be a significant risk factor for preterm birth and adverse neonatal outcomes (207,208).

Increasing preclinical evidence shows that stem cell therapy can provide significant neuroprotective effects for the preterm brain (209,210). In recent years, research has focused on fetal derived mesenchymal stem cells (MSCs) and umbilical cord blood (UCB) cells because of their easy accessibility, low immunogenicity and immunosuppressive potential (211). Results of one clinical trial suggested that fresh autologous UCB cells was safe and benefited neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy (212). In clinical trials of CP, administration of processed UCB cells into the cerebrospinal fluid was generally safe and effective at improving the gross motor and cognitive functions (213-216). However, there remain many questions regarding the use of stem cell therapy, including the most effective stem cell type, the optimal dosage, timing and route of administration, the ideal patients who would benefit from therapy, the mechanisms of stem cell therapy.

Cumulative effects of multiple neuroprotective strategies

Many perinatal management strategies have individually been shown to be neuroprotective to EPIs; however, few studies been done on the cumulative effects of these strategies when used in combination. Recently, an observational study evaluated the cumulative effects of 4 evidence-based strategies (ACS, antenatal $MgSO_4$, DCC ≥30 s, and normothermia on admission) in reducing the risk of death and/or severe neurological injury among EPIs (217). The results demonstrated that rates of death and/or severe neurological injury varied based on exposure to assessed evidence-based strategies: none, 34%; any 1, 27%; any 2, 20%; any 3, 18%; and all 4, 14%. Additionally, the pairwise combinations of ACS plus DCC and ACS plus normothermia were associated with the lowest rates of death and/or severe neurological injury (217). Another observational study also reported a reduction in the incidence of death and/or severe neurodevelopmental impairment in EPIs treated with both ACS and $MgSO_4$, when compared to those exposed to ACS alone (218).

Conclusions

In this review, we present a range of evidence-based perinatal managements (*Table 2*) shown to improve neonatal outcomes among EPIs. There are still numerous unanswered questions in the development of some emerging therapies for clinical practice. In addition, while new therapies are being investigated, a broader understanding

Table 2 Major morbidities and corresponding evidence-based management strategies in EPIs

Affected organ or system	Morbidities	Management strategies
Pulmonary	RDS, AOP, pneumothorax, BPD	ACS, DCC, NIV, PS, caffeine
Cardiovascular	PDA	Conservative non-intervention management, indomethacin, ibuprofen, TCPC
Immunologic	EOS, LOS	ACS, antibiotics, CRP and PCT monitoring
Gastrointestinal or nutritional	NEC, growth restriction	ACS, DCC, breast milk, nutrient fortifiers
Central nervous system	Neurodevelopmental impairment, IVH, PVL, HIE, CP	ACS, $MgSO_4$, DCC, caffeine, EPO, MSCs
Ophthalmologic	ROP	Lower initial FiO_2, lower SpO_2

EPI, extremely preterm infant; RDS, respiratory distress syndrome; AOP, apnea of prematurity; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; EOS, early onset sepsis; LOS, late onset sepsis; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; HIE, hypoxic-ischemic encephalopathy; CP, cerebral palsy; ROP, retinopathy of prematurity; ACS, antenatal corticosteroids; DCC, delayed cord clamping; NIV, non-invasive ventilation; PS, pulmonary surfactant; TCPC, transcatheter PDA closure; CRP, C reactive protein; PCT, procalcitonin; EPO, erythropoietin; MSCs, mesenchymal stem cells.

of current strategies and their effective application may also lead to improvement in outcomes for EPIs.

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