Nutrition strategies to prevent short-term adverse outcomes in preterm neonates

Samantha Rodriguez, Diomel de la Cruz, Josef Neu

ABSTRACT
With preterm neonates surviving earlier gestational ages, comorbidities such as bronchopulmonary dysplasia, retinopathy of prematurity, delayed neuronal development, intestinal injury, osteopenia, and parenteral nutrition-associated liver disease have become more common. This has been a topic of much deliberation and research to identify mitigation strategies. We explore nutrition approaches and risk factors for each condition individually, even though some strategies may overlap due to similar disease mechanisms. These conditions have long-lasting effects on preterm neonates, calling for ongoing assessment of practical and adjustable interventions. Recent studies elucidate the utility of nutrition optimization for the prevention of bronchopulmonary dysplasia, retinopathy of prematurity, delayed neuronal development, intestinal injury, osteopenia, and parenteral nutrition-associated liver disease. Specifically, amino acids, lipids, breastmilk, and Vitamins A, D, and E have been shown to effectively mitigate the risk these common morbidities affection preterm neonates. Further studies are needed to identify targeted ranges of macronutrients, vitamins, and minerals essential to the varying gestational ages and high-risk populations.

INTRODUCTION
Neonatal intensive care over the past several decades has resulted in the survival of infants at gestational ages previously not thought possible. Along with this improved survival, the most immature of these infants have a much higher likelihood of developing adverse effects during their hospitalisation, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), neurodevelopmental impairments necrosising enterocolitis (NEC), and osteopenia of prematurity, and parenteral nutrition-associated liver disease (PNALD). Various strategies have been proposed and are areas of research for treatment of these problems. It is better to be proactive rather than reactive; hence, there is a great interest in preventative strategies. In this review, we will focus on nutritional preventative and therapeutic approaches that have been studied and suggest future strategies to make these more personalised and precision based. Six adverse outcomes will be reviewed (see figure 1). It is important to understand that these have significant overlap and may occur concurrently, especially in preterm infants. Similarly, nutritional preventative strategies will exhibit overlap. We will present these separately.

BRONCHOPULMONARY DYSPLASIA
BPD is a chronic lung disease that primarily affects premature infants, especially those born before 28 weeks of gestation or with very low birth weight (VLBW). BPD typically develops within the first month of life, but can persist for months or even years after birth, depending on the severity. Nutrition plays a critical role in the prevention and management of BPD. Many infants with BPD exhibit growth failure due to poor nutrition, and many get into a vicious cycle where problems in the lungs affect feeding. These feeding problems in turn compromise lung healing and growth. A critical concept with BPD is that a proactive rather than reactive approach from the first day after birth can aid in the reduction of respiratory morbidity. Appropriate fluid management, early parenteral nutrition (PN) with protein and lipids, and early enteral feeding have been shown to reduce the development of BPD.

A comprehensive literature review determined that infants with established BPD should receive a fluid intake of not more than 135–150 mL/kg/day and an energy intake of 120–150 kcal/kg/day. Difficulties providing low volumes with high energy remain challenging and are the genesis of extrauterine growth restriction and poor lung healing in these infants. Therapies such as fluid restriction, diuretics and corticosteroids can negatively impact postnatal growth.

In terms of preventative strategies, optimising nutrition shortly after birth provides benefits. A retrospective study in China evaluated the relationship between early PN intake and BPD development in preterm infants of less than 32 weeks gestational age who could not receive enteral nutrition within 1 week after birth. The study population included...
79 infants with BPD and 73 infants without BPD. Infants with BPD had lower intake of amino acids and lipids and a lower proportion of calories provided by amino acids and lipids in the first week after birth, suggesting an association between early PN intake and the development of BPD. A large cohort study of extremely preterm infants in Stockholm evaluated nutritional interventions in the early stages of postnatal life. The study excluded infants who died before 10 days of life, had chromosomal anomalies or other significant anatomic malformations, specifically those requiring abdominal surgery within 1 week of life. This study identified a significant association with energy and protein intake with reduced risk of BPD and decreased days of mechanical ventilation during postnatal days 7–27. These results persisted despite adjustment for episodes of sepsis or NEC that may have contributed towards nutritional deficits in early postnatal life. Identification of preventive nutrition modalities that may play a role in risk mitigation in the preterm neonatal population should be of the utmost priority in the care of this highly susceptible group.

There has been a traditional concern for early introduction of intravenous amino acids, lipids, and glucose. Nagel et al studied the feasibility and safety of enhanced early PN (early initiation of intravenous lipid emulsions and faster advancement of glucose infusion rate) during the first week of life for VLBW preterm infants. 90 VLBW preterm infants (<32 weeks gestational age at birth), stratified by gestational age and randomised to enhanced nutrition versus a standard PN protocol. Enrolled infants were stratified by gestational age groups and randomised to either the enhanced nutrition protocol (intervention group) or the standard PN protocol (standard group). The intervention group received higher weekly mean caloric intake (102.6 (SD 24.9) kcal/kg/day vs 89.7 (SD 30.2) kcal/kg/day; p=0.001) and higher mean caloric intake on days of life 2–4 (p<0.05 for all). Both groups received the recommended protein intake (≥4g/kg/day). Thus, the enhanced group received more lipids and glucose. Use of the enhanced nutrition protocol during the first week after birth resulted in increased caloric intake and was feasible with no evidence of harm. In a follow-up study of this cohort, neurodevelopmental outcomes were evaluated. Higher enteral energy and protein intake, regardless of randomisation group were associated with faster processing speed at 4 months CA (p=0.02 for both). Enhanced early PN was not associated with improved neurodevelopment; however, first-week enteral caloric and protein intake were associated with improved speed of processing. There may also be individual nutrients helpful in the prevention of BPD. Here a few of these are discussed.

**Docosahexaenoic acid**

Docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid (LCPUFA) with putative anti-inflammatory properties, is an enzymatic product of linolenic acid after desaturation and elongation with specialised enzymes. A meta-analysis of several randomised clinical trials on DHA supplementation found that enteral supplementation with high-dose DHA was not associated overall with BPD. However, DHA had a positive association with BPD in the randomised controlled trials (RCT) that used a more stringent BPD definition based on pulse oximetry.
readings at 36 weeks corrected gestational age. This led to the conclusion that high-dose DHA supplementation should not be recommended to prevent BPD in very preterm infants. In another study on infants under 29 weeks gestational age, supplementation with arachidonic acid (AA) and DHA was safe and significantly reduced respiratory support duration and lower oxygen demand (FiO2). There were no clinically significant differences in incidence of BPD and other major morbidities between the treatment groups. While a balance between AA and DHA may significantly impact on BPD prevention, a target ratio is not currently known but should be explored in future research.

**Vitamin A**

Vitamin A is crucial in fostering proper lung development and maintaining the structural integrity of respiratory tract epithelial cells. Neonatal vitamin A status on birth correlates notably with an elevated susceptibility to chronic lung disease. An in-depth examination conducted by a Cochrane review delved into randomised trials centred on vitamin A supplementation and its impact on the necessity for supplemental oxygen at 1-month postbirth and at 26 weeks of postmenstrual age. Vitamin A supplementation to infants of extremely low birth weight was associated with a marked reduction in both mortality and oxygen requirement within the first month after birth and oxygen necessity among survivors by the 36th week of postmenstrual age. This latter effect was particularly pronounced among infants with a birth weight below 1000 gs. Vitamin A was administered in repetitive doses via the intramuscular route. The authors of the review concluded that the decision to incorporate repeated intramuscular vitamin A administration into clinical practice, aimed at preventing chronic lung disease, hinges on a complex interplay of factors encompassing the local incidence of such an outcome, the significance attributed to achieving a modest reduction in its occurrence, the absence of substantiated ancillary advantages and the ethical aspects of treatment. The review also highlighted that data pertaining to the long-term neurodevelopmental status failed to reveal any discernible evidence of either benefit or detriment stemming from the intervention.

A recent scholarly article undertook a comprehensive assessment of the existing literature in relation to the nutritional challenges encountered by patients with established bronchopulmonary dysplasia (BPD). In addition to thoroughly exploring enteral nutrition management and monitoring techniques, the article presents a pragmatic framework for interdisciplinary nutritional care, extrapolating from clinical insights gained at a single centre. While presenting general recommendations encompassing fluid administration, energy provision, lipids, modular components, as well as vitamins and minerals, the article underscores the intrinsic heterogeneity characterising this patient cohort. Consequently, further investigative efforts are imperative to fill the gaps in our understanding, and personalised strategies are pivotal in enhancing the long-term outcomes of these particularly vulnerable neonates.

**RETNOPATHY OF PREMATURITY**

In preterm infants, retinal blood vessel development is interrupted because the retina’s blood vessels are not yet fully developed. Many factors associated with prematurity can lead to abnormal vessel growth, which may cause vision loss or blindness due to retinal detachment if not treated. ROP is defined as retinal abnormalities that occur during development due to oxygen disturbances and nutrient supply after preterm birth. Additional evidence suggests that metabolic disturbance is a significant and underevaluated risk factor in disease pathogenesis. Nutritional and hormonal supplementation may relieve metabolic stress and improve retinal maturation. As for nutritional strategies for preventing and treating ROP, several approaches have been studied, including breast milk, omega-3 fatty acids, antioxidants such as vitamins C and A, and amino acids such as arginine and taurine. Here we will examine these in more detail.

**Parenteral and enteral nutrition**

A Swedish population-based study on 498 extremely premature infants demonstrated that higher energy intake by way of fats and carbohydrates was associated with a significantly decreased prevalence of ROP. While unable to be fully assessed in the study, this relationship was found among those with increased energy intake by 10 kcal/kg/day and suggested that the lower initial recommendations of 110–130 kcal/kg/day may be insufficient for extremely premature infants. A recent retrospective cohort study of 11 139 premature infants in the Swedish National Registry for ROP compared infants receiving PN and those transitioning to enteral feeds within 14 days of life. This study demonstrated an increased risk of ROP and a shortened time frame to initiation of ROP therapy in the PN group compared with those transitioned to enteral feeds. When discussing enteral nutrition, exclusive Mothers’ own milk (MoM) has demonstrated a lower incidence of ROP relative to formula-fed infants.

**Long-chain polyunsaturated fatty acids**

LCPUFA are critical for the maturation of the brain and retina. They have anti-inflammatory, antioxidant and anti-angiogenesis effects. Supplementation of enteral LCPUFA might mitigate the incidence of ROP in these infants. A meta-analysis of 9 eligible studies involving 2382 infants showed that supplementation of enteral LCPUFA to preterm infants less than 32 weeks gestational age did not reduce ROP incidence. A multicentre RCT evaluating a decrease in the severity of ROP with supplementation of AA and DHA in 209 extremely premature infants less than 32 weeks gestation decreased the severe ROP risk by 50%. Fish oil-containing PN was also found...
to have a lower risk of ROP development in a retrospective cohort study.\textsuperscript{17}

**Amino acids**
ROP is a retinal vascularity pathology in premature neonates that threatens sight. The direct mechanism of serum amino acids on the development of ROP remains unclear at this time, but studies have demonstrated certain amino acids to be linked to ROP progression. A randomised case control of 55 premature neonates under 32 weeks gestation identified an inverse relationship between serum arginine and glutamine levels and ROP severity. There was also a negative correlation between the stage of ROP and serum aspartate levels. However, the group with worsened ROP also had a significantly lower mean gestation age, which may have affected the outcome.\textsuperscript{18} Additionally, a case–control study further demonstrated elevated citrulline and aminoadipic acid in neonates with ROP.\textsuperscript{19} Contrary to these findings, supplementation using a dipeptide of glutamine and arginine inhibited vascular endothelial growth factor expression and, therefore, neovascularisation in oxygen-induced retinopathy murine models.\textsuperscript{20}

**Vitamin E**
Numerous studies have reported the possible involvement of reactive oxygen species-induced damage in relation to supplemental oxygen use, inflammation and immature antioxidant defence in the development of ROP. Various antioxidants effectively prevented the worsening of BPD and ROP in animal models. Most of the available studies on vitamin E prevention were performed over 20 years ago in infants of approximately 30 weeks gestation and demonstrated variable results.\textsuperscript{21} Whether vitamin E would be safe and efficacious in the micropremies of the 2020s era awaits additional studies.

**Vitamin A**
Sufficient delivery of vitamin A has emerged as a requisite element in fostering time-dependent and precise eye development, a phenomenon substantiated through investigations in mouse models. This significance becomes particularly apparent in Pitx2 expression, a homeobox gene that assumes a pivotal role. Within this context, the Pitx2 gene emerges as a critical determinant in orchestrating the closure of the optic fissure, the retina’s intricate folding and the broader anterior developmental processes within the ocular domain. The absence of adequate vitamin A in murine subjects has been associated with notable anomalies, including coloboma manifestation and augmented retinal folding. This pathological cascade is attributable to the deficient dissolution of the basal lamina layer, an eventuality further underpinned by the depletion of cellular entities bearing the hallmarks of cyclin D1 positivity, as well as the compromised presence of N-cadherin and β-catenin, pivotal cell adhesion molecules.\textsuperscript{22}

Moreover, the proactive supplementation of active vitamin A has exhibited tangible benefits in mitigating the occurrence and severity of ROP among VLBW neonates. The collective evidence underscores an impressive 88% reduction in the risk of severe ROP development, emphasising the beneficial impact of such supplementation in a highly vulnerable patient demographic.\textsuperscript{23}

**NEURONAL DEVELOPMENT**
Preterm infants are at high risk for neurodevelopmental delays.\textsuperscript{24} Several nutritional approaches have been proposed and studied for optimising neurodevelopment and preventing complications such as poor growth associated with poor neurodevelopmental outcomes. Early and effective nutrition resources are imperative for neurological development in the premature neonatal population.

**Enteral and PN**
Early proactive nutrition of the preterm infant is almost exclusively parenteral during the initial stabilisation period specifically prioritising high protein intake.\textsuperscript{25} An observational study of 100 VLBW neonates between 27 and 31 weeks gestation identified a significant difference in neonatal head circumference between enteral and PN. High amino acid contents of enteral nutrition were positively correlated with the development of the corpus callosum, caudate heads bilaterally, cerebellar vermis and cerebellum while those of PN were negatively correlated. Interestingly, higher protein intake was associated with smaller left caudate head and cerebellar vermis size among the PN subgroup. These findings were controlled for confounders including NEC, culture-proven sepsis and BPD.\textsuperscript{25} However, a separate retrospective cohort study identified a positive relationship between high parenteral amino acid intake, defined as 1.5g/kg/day or greater, and neurodevelopment outcomes at 2 years of age among the VLBW preterm infants. This was found in conjunction with higher caloric intake being associated with decreased hospitalisation, ventilator and supplemental oxygen requirement durations.\textsuperscript{26}

**Breast milk and formula**
MoM remains the most beneficial enteral nutrition source for neurodevelopment in relation to growth and development\textsuperscript{27} and structural connectivity.\textsuperscript{28} The benefits between human donor milk (HDM) and formula, when MoM is unavailable, remains a point of contention in the literature. A single-centre observational cohort study comparing preterm formula, MoM and HDM demonstrated a significant reduction in cognition at 1-year and 2-year follow-ups in the HDM group compared with the preterm formula and MoM groups.\textsuperscript{29} A double-blind RCT including 4 neonatal intensive care units (NICUs) with 840 infants found no statistically significant difference in neurodevelopment using Bayley-III cognitive composite scores, language or motor scores.\textsuperscript{30}
Fatty acids

Fatty acid oxidation has been demonstrated to increase significantly throughout gestation as a significant resource for growth in development in late-stage pregnancy making premature neonates at greater risk for restricted growth with inadequate lipid supplementation. In a retrospective cohort study of 67 VLBW neonates hospitalised at a level IV NICU, there was a statistically significant positive correlation between cumulative lipid intake and cerebellar and brainstem volume at 4 weeks of life. It was not statistically significant, but the positive relation between cortical brain volume and fatty acid intake is worth mentioning. No significant association was found in relation to carbohydrate or protein intake. However, this study combined data from both enteral and parenteral sources which may have skewed the results. However, a retrospective study on extremely premature infants less than 27 weeks gestation demonstrated statistically significant positive associations between total daily energy and protein intakes with head circumference. The CLIMB study is a large, two-centre RCT that evaluated the use of complex milk lipids including gangliosides and phospholipid supplementation in infants greater than 32 weeks gestation (N=1500) had no significant change in head circumference growth rates at 12 months follow-up. Additional studies are necessary for the further standardisation of nutrition and the optimisation of neurological development.

Amino acids

Enteral amino acid supplementation has been associated with improved brain volume. A single-centre cohort study compared the difference in head circumference and cognitive adaptive skills in the neonatal population directly correlated to the quantity of amino acids in their early nutrition regimens. Cognitive-adaptive scores in these cases differed from 98.3 in the high amino acid group and 91.9 in the low amino acid group by 18 months in VLBW neonates. There was also a decreased risk of borderline disability in cognitive-adaptive skills, language, social and generalised developmental skills in the higher amino acid content group. Specific amino acids may also be of particular benefit. Early enteral glutamine supplementation for 1-month postdelivery was shown to have increased white matter, hippocampal and brain stem volumes on school-age follow-up of preterm neonates less than 32 weeks gestational age. This is thought to be due to improved gut integrity and inhibition of bacterial translocation, resulting in a decreased risk of systemic infection and subsequent white matter injury.

Lactoferrin

A Cochrane Systematic Review evaluating six RCTs demonstrated lactoferrin supplementation to enteral feeds minimised late-onset sepsis and stage II and III NEC in preterm infants, however, the evidence has been reported as low quality. The ELFIN RCT that evaluated 2203 preterm infants did not identify a reduction in infection incidences, morbidity or mortality. The efficacy of lactoferrin use in preventing NEC remains a current gap in the literature that should be considered in a standardised approach.

Formula, breast milk and fortification

MoM has been documented and well studied as one of the most protective feeding regimens available for risk reduction for developing NEC. A meta-analysis of 42 studies including cohort, cross-sectional and case-control studies identified a nearly threefold increase risk of development of NEC in formula-fed infants compared with those who were breastfed. However, at a baseline, there were more infants in the formula group compared with the MoM group at a nearly 5:1 ratio, which may have influenced the analysis. A quality improvement project spanning 14 NICUs demonstrated a statistically significant reduction in NEC incidence associated with HDM compared with formula from 5.1% to 2.9%. A multicentre RCT comparing human milk with human milk-based fortification to human milk with bovine-based fortification further demonstrated a reduction in NEC in the human milk fortifier compared with the bovine-based group. However, in this study, the fortification began at inequitable times of feed progression (at 40mL/kg/day for human milk-fortified group vs 100mL/kg/day for the bovine milk-fortified group). Additionally, when MoM was unavailable the bovine-fortified group received formula, which may have influenced the outcomes discussed. O’Connor et al conducted a multicentre RCT comparing human milk-based versus bovine-based fortification to human milk without the addition of formula and with fortification initiation simultaneously. In this study, there was no significant difference in the risks of NEC, feeding interruptions, growth and mortality between the two types of fortification.

Standardisation of feeding

Standardised feeding guidelines bring notable advantages, encompassing cost reduction in PN and enhanced weight gain, all while sidestepping escalated susceptibility to NEC or sepsis. A Cochrane review on the optimisation of feeding regimens through a standardised approach...
with more rapid rate of increased enteral nutrition was associated with nephrocalcinosis, hypercalciuria, abdominal distention. A dose of 3.75 mmol/kg/day of calcium and 2.5 mmol/kg/day of phosphate if both effective for bone mineralisation without the side effects of high-dose calcium treatment. Vitamin D supplementation, even low dose of 200 IU/day, has been shown sufficient at reduction in osteopenia of prematurity. These interventions should be considered feasible, modifiable factors to promote proper bone development in preterm neonates.

**Human milk and formula**

Standardising nutrition within the NICU has proven valuable for averting long-term issues like osteopenia of prematurity. When comparing MoM to preterm formula, both with equivalent phosphorus supplementation, no substantial difference in bone mineralisation was found when accounting for weight variability between groups. Conversely, a 20-year follow-up RCT indicated that greater whole-body bone mass was linked to breastfed infants rather than those on formula. Moreover, the proportion of human milk per kilogram fed correlated with enhanced bone mineralisation, regardless of higher calcium and phosphorus content.

**PN-ASSOCIATED LIVER DISEASE**

PNALD is a condition of neonates characterised by cholestasis, steatosis and potentially liver dysfunction and cirrhosis. The underlying pathophysiology leading to PNALD remains unclear, but several theories have been proposed including infection, lipid administration resulting in increased cytokine release, bacterial translocation in the setting of delayed enteral feeds. While PNALD may be reversible, if left untreated, is associated with liver fibrosis, liver failure and death in the most extreme cases. As such, efforts must be made to promote early enteral nutrition when able and identify protective measures for reducing the incidence of PNALD.

**Lipid emulsions**

Parenteral soybean oil, medium chain triglycerides, olive oil and fish oil lipid emulsions (SMOF) have been shown beneficial in the prevention of PNALD in the premature infant population relative to medium and long chain fatty acids emulsions. A multicentre RCT identified an impressive, statistically significant reduction in the incidence of PNALD, specifically cholestasis, among those receiving SMOF versus medium and long chain lipids (13.7% vs 21.2%, relatively). While the individual components have protective effects on the liver relatively to medium and long-chain lipids, the combination of SMOF lipids has an even more significant improvement in hepatic tolerability when compared with the individual components.

**Amino acids**

Certain amino acids have demonstrated protective effects on the liver concerning the incidence of PNALD. Wang
et al conducted an RCT evaluating the effect of glutamine supplementation on PNALD in preterm infants. It was found that supplementation of 0.5g/kg/day of glutamine significantly reduced gamma-glutamyl transferase and alkaline phosphatase.66 However, it remains unclear due to small sample size and lack of additional supportive studies available to determine the clinical significance of glutamine supplementation at this stage. Larger power studies should be done to evaluate the efficacy of hepatoprotection with parenteral glutamine supplementation further.

SUMMARY
As preterm neonatal survivability increases, so does the prevalence of associated complications such as BPD, ROP, delayed neuronal development, intestinal issues, oesopha-gena and PNALD. Nutritional strategies offer practical interventions that can potentially alleviate the severity of these complications in later life. Emphasis should be placed on using MoM or human milk whenever feasible. Specific nutrients, modern lipid formulations, and optimised vitamin and mineral profiles also deserve careful attention in catering to the unique nutritional needs of this high-risk group. Optimisation of amino acid content, utilisation of SMOF lipids and addition of vitamin A, D and E should be implemented in clinical practice to mitigate the risk of these common comorbidities among premature neonates. Future areas for investigation include identification of goal ranges in high-risk populations such as preterm neonates with congenital heart disease, gastrointestinal pathology and intrateternal growth restriction. The horizon holds exciting prospects where machine learning, artificial intelligence, multomics intersect, offering avenues for identifying connections between nutrition and various disease states. This, in turn, may provide a personalised approach and precision nutrition these neonates. In this evolving landscape, technology and science intertwine to illuminate a path towards enhanced understanding and intervention for a healthier future.67–70

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