REVIEW

Paediatric parenteral nutrition: current issues

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ABSTRACT

Parenteral nutrition transformed the prognosis for infants and children with intestinal failure. Soon after its introduction into clinical care 50 years ago, parenteral nutrition was also rapidly adopted for use in the preterm infant, where immaturity of gastrointestinal motor function precluded enteral feeding. Preterm infants subsequently became the single largest group of patients to be fed in this way. Although the development of scientific knowledge and the lessons of clinical experience have reduced the risk of complications, some of the problems and difficulties associated with this form of nutritional support remain challenging. These include central venous catheter-related sepsis, thrombosis, liver disease, bone disease and metabolic disturbance. In an initiative to promote best practice, guidelines on parenteral nutrition were first published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and collaborating organisations in 2005. These were constructed following a thorough review of the scientific literature, allowing a series of evidence-based recommendations to be made. The exercise was repeated just over 10 years later and updated guidelines published in 2018. This review summarises key elements from the new guideline, with a focus on what has changed since 2005.

INTRODUCTION

The history of parenteral therapy extends for more than four centuries but parenteral nutrition (PN) as we know it today first came into use in the 1960s^{1,2} as a life-saving intervention for patients with intestinal failure. Huge progress in the last 50 years has made this mode of nutritional support both safe and effective. A guideline on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) supported by the European

Key messages

- ▶ Taurodine is effective in preventing central venous catheter-related sepsis and should be used during long-term catheter use.
- ▶ For parenteral nutrition (PN) lasting longer than a few days, pure soybean oil emulsions should no longer be used and composite emulsions with or without fish oil should be the first choice treatment.
- ▶ Consider withholding PN including amino acids for 1 week in critically ill children and use an isotonic intravenous fluid to 'maintain hydration' in this group of patients especially during the first 24 hours.
- ▶ PN solutions may be administered through a terminal filter: lipid emulsions or all in one mixes through a membrane pore size of 1.2–1.5 µm, aqueous solutions through a 0.22 µm membrane.
- ▶ Light protection is recommended for both PN bags and administration sets.
- ▶ Standard PN solutions should be used over individualised solutions in the majority of paediatric and newborn patients, including very low birthweight premature infants.

Society of Paediatric Research (ESPR) was published in 2005.³ This was recently revised following a review of current literature,⁴ with updates including the use of Taurolock to prevent central venous catheter (CVC)-related sepsis and the role of new multicomponent lipid emulsions. Stronger recommendations have been given with regard to the use of inline filtration and photoprotection of PN fluids and advice on energy, fluid, electrolyte, macronutrient and micronutrient intake updated. In addition, the large PEPaNIC multicentre trial of early or delayed PN in intensive care⁵ prompted considerable debate about timing of initiation of PN in critically ill children.⁶ The 2018 guideline forms the basis for this review of what is new in paediatric PN. Readers are referred

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to the full published guideline for details of how it was developed, the literature reviewed and the strength of evidence on which recommendations were based.

ENERGY

In the absence of enteral intake, PN has to meet all nutritional needs including energy for basal metabolic rate (BMR), physical activity, growth, and correction of pre-existing malnutrition. Overfeeding can have negative effects, and energy supply during intensive care aims to meet resting energy requirements. In children, BMR (the energy needed to perform basic, life-sustaining functions) cannot be calculated and resting energy expenditure (REE) is used as an alternative. Few centres have ready access to indirect calorimetry to measure REE, and it is recommended that the Schofield equation based on weight is used. In underweight children, both height and weight should be factored as this is less likely to underestimate REE compared with indirect calorimetry.⁷ In 2001, a number of different international agencies proposed changes to energy requirements for children: on average, 18% lower for boys and 20% lower for girls aged <7 years; 12% and 5% lower, respectively, for boys and girls aged 7–10 years and 12% higher above 12 years.⁸

For preterm infants, new studies have shown an improvement in postnatal growth when PN is started earlier,⁹ although current practice is very variable. A preterm infant has to receive 45–55 kcal/kg/day in the first day, aiming for a weight gain of 17–20 g/kg/day. The total energy requirement for an enterally fed infant is approximately 110–135 kcal/kg/day compared with 90–120 kcal/kg/day in PN dependency due to reduced needs for thermogenesis and lower stool energy loss.¹⁰

Findings of a large randomised controlled multi-centre trial (the PEPaNIC study) conducted in three intensive care units in Belgium, the Netherlands and Canada and enrolling 1440 ill newborns, infants and children,⁵ have prompted important changes in recommendations. This study suggested that withholding PN for up to 8 days when compared with early initialisation (within 24 hours after intensive care unit admission) reduced the number of new infections, the time on a ventilator, incidence of kidney failure and the length of stay in both paediatric ICU (PICU) and hospital; no change in mortality was seen. However, more than 77% of patients allocated to late PN were discharged by day 8 without having received any PN, raising questions about initial indications. A possible mechanism relates to the shortening of chromosomal telomeres with each cell cycle, known to be accelerated in severe illness and associated with increased morbidity and mortality.¹¹ Studies have shown that in critically ill children, early initiation of PN is associated with further shortening.¹² The guidelines make a conditional recommendation that for critically ill patients in all age groups, withholding PN for 1 week while providing micronutrients should be considered.⁵

Limitations of the PEPaNIC study include heterogeneity of both the patients and the management of nutrition and glucose control. The optimum timing of initiation of PN therefore remains unknown, although for patients with brain trauma, all studies have shown that early caloric intake reduces both mortality and length of ICU stay.¹³

AMINO ACIDS

Requirement for amino acids is lower with parenteral than enteral feeding. In preterm infants, starting amino acids in the first day of life has been associated with a reduction in sepsis and time to regain birth weight.¹⁴ The recommendation in this age group is to start with at least 1.5 g/kg/day of amino acids, while the maximum intake has been reduced from 4.0 to 3.5 g/kg/day. For other age groups, recommendations remain the same at 1.5–3.0 g/kg/day for term infants, a minimum of 1 g/kg/day for 1 months–3 years; 1–2 g/kg/day for 3–12 years and adolescents.¹⁵

There is little new information with regard to specific amino acids, although it has been shown that a dose of cysteine above 50–75 mg/kg/day is not beneficial for preterm infants. The prior recommendation against supplementary glutamine in the preterm is complemented by new studies showing no benefit in children <2 years.¹⁶ There is no new data on tyrosine, taurine or arginine intake.

LIPIDS

Highlighted advantages of multicomponent lipid emulsions containing soybean oil, medium chain triglycerides, olive and fish oil (SMOFlipid) include higher vitamin E and less phytosterol content.¹⁷ The optimal time for starting lipid in the newborn has been controversial, but current advice is that initiating soon after birth will improve growth and developmental outcomes⁹; dose recommendations are unchanged.¹⁸ The 2005 ESPGHAN/ESPEN guideline stated that there was no evidence to support the advantage of any one particular lipid emulsion,³ but recent studies have shown that SMOF lipid is better than pure soybean oil (SO) in reducing sepsis episodes,¹⁹ in offering more balanced nutrition and in preventing intestinal failure associated liver disease (IFALD).²⁰ Pure SO emulsion can still be given for the first few days of PN but should be changed to a composite formula if PN is required for longer periods of time.

Previously, the management for cholestasis was to reduce or even stop lipid intake; however, this may affect neurodevelopment in preterm infants²¹ and cause essential fatty acid deficiency. A lower dose of pure fish oil (FO) or SMOFlipid for several months may improve IFALD,²² but while cholestasis and liver function tests improve with FO/SMOFlipid, no changes are seen in the degree of fibrosis.²³ Some centres now use pure FO as a rescue treatment when cholestasis is severe, although 10% pure FO emulsion

is not registered for paediatric use in Europe. There are no published trials investigating the best timing for starting lipids in critical illness, but undoubtedly lipids are necessary to avoid fatty acid deficiencies. As SMOFlipid has more antioxidant effect and are less proinflammatory and immunosuppressive compared with pure SO, it may be preferable during intensive care.²⁴ Recent case reports suggest a possible role for lipid emulsions in treatment for drug toxicity.²⁵

CARBOHYDRATES

The PEPaNIC study has undoubtedly fostered caution with regard to energy intake.^{5 26} New guidance²⁷ proposes lower carbohydrate intake to avoid hyperglycaemia during increased endogenous glucose production. Dividing the period of acute illness into acute, stable and recovery phases, carbohydrate intake is gradually increased from one phase to the next until reaching full requirements.

Term and preterm newborns receive a lower amount of glucose in the first day of life with gradual increase from day 2. In the case of acutely unwell newborns, the same principle of a lower glucose intake applies, continuing with the same intake as on day 1, with glucose monitoring to help maintain normoglycaemia. Blood gas analysers validated for glucose measurement offer rapid and accurate results.²⁸ Hyperglycaemia is associated with increased morbidity and mortality especially in critically ill children and preterm infants and recognition and appropriate management are extremely important. For ill newborns and PICU patients, repeated blood glucose concentrations >10 mmol/L (180 mg/dL) can be controlled with insulin therapy.²⁷ The effects on outcome of hypoglycaemia are difficult to define in critically ill children and there are no clear conclusions regarding effect on neurodevelopment in preterm babies. It is recommended that ICU patients should avoid repetitive or prolonged glucose concentrations of ≤ 2.5 mmol/L (45 mg/dL).

FLUID AND ELECTROLYTES

The majority of recent studies on fluid and electrolyte requirements relate to needs of the preterm infant. For phase 1 (transition: characterised by an initial relative oliguria followed by a diuretic phase with natriuresis, and ending when the maximum weight loss has occurred), the new guideline²⁹ defines acceptable weight loss in term newborns as up to 10% between day 2–5 of life, and 7%–10% for ‘extremely’ and ‘very low birth weight’ (VLBW) infants. In response to the recognition of refeeding syndrome (hypokalaemia, hypophosphataemia and hypercalcaemia) in VLBW infants receiving high doses of amino acids and energy, sodium and potassium are recommended from the first day of life providing renal function is stable.³⁰ In addition, chloride should be avoided in the first days of life to minimise the risk of metabolic acidosis. Compared with the previous recommendations, the volume of

fluid for term newborns on day 1 of life has been reduced from 60 to 120 to 40–60 mL/kg/day. Low birthweight preterm are now divided into two groups according to weight: 1000–1500 g and <1000 g with some restriction in the fluid intake for 1000–1500 g group. For phase two (intermediary: characterised by a high urinary excretion of sodium), the new guidance recommends a higher limit for sodium intake in preterm <1500 g of up to seven mmol/kg/day, with a target age to recover birth weight changed from 5 to 15 to 7–10 days.²⁹ After the neonatal period, maintenance fluid volume is still calculated using the Holliday-Segar method with the proviso that every patient should have their underlying diagnosis and condition taken into account.

Major changes are for postoperative and critically ill children where a high risk of hyponatremia was established in a meta-analysis³¹ that compared hypotonic versus isotonic maintenance fluids. New evidence indicates that isotonic fluids should be used at least for the first 24 hours of intravenous hydration. In patients with high stoma losses, where the electrolyte excretion is very high, sodium chloride can be replaced in the PN by sodium lactate or sodium acetate in order to reduce acidosis. Publications regarding continuous low-dose ranitidine infusions in PN for decreasing gastric hypersecretion and faecal output were published in the past and the new guidelines²⁹ also refer to this treatment option.

MICRONUTRIENTS

Iron requirements are increased in PN-dependent patients due to higher losses and increased demands. Side effects of iron include overload and increased risk of infection, making enteral iron the first choice if tolerated. New studies have shown that intermittent infusions will have the same effect as daily regular doses added to the PN.³² The dose recommendation for preterm infants has been increased from <200 to 200–250 μ g/kg. Whereas iron sucrose seems to be the safest option for infusion; this currently has approval only in USA. For zinc, the recommended dose range in the preterm infant is now slightly lower at 400–500 versus 450–500 μ g/kg/day with an emphasis on increased requirements with high stoma losses.

The dose for copper in preterm infants has increased from 20 to 40 μ g/kg/day based on new data, with no changes for term infants and children. There has also been an important change in relation to iodine since the previously recommended dose of 1 μ g/day was found to be insufficient in preterm babies (now increased to 1–10 μ g/kg/day). Doses of iodine up to 30 μ g/kg/day having been investigated in randomised trials; no changes in the dose for term infants and children were suggested. Low selenium was found to be associated with bronchopulmonary dysplasia in the preterm and the recommended dose increased from 2 to 3 to 7 μ g/kg/day, with no change for term infants

and children (2–3 ug/kg/day; maximum 100 ug/day). Serum concentration should be monitored during long-term PN and in patients with renal impairment.³² The current commercially available preparations do not meet these recommendations for copper and zinc and have the minimum required amount of selenium and iodine mainly in the case of preterm babies making the monitoring with blood tests essential. Given the potential neurotoxic effects of manganese, monitoring is recommended particularly if there is cholestasis compromising biliary excretion.

Ca, PO₄, Mg

The importance of parenteral Ca, PO₄ and Mg for growth and bone mineralisation is discussed in detail.³³ Again, changes compared with the previous recommendations are mainly seen for preterm and term newborns. In the preterm, the risk of hypophosphataemia and hypercalcaemia is influenced by early amino acid intake.³⁴ The utilisation of PO₄ for growth in the first days of life has been extensively investigated in recent years. An early intake of phosphorus and a ratio Ca:PO₄ below 1 (0.8–1) is recommended to reduce the risk of electrolyte imbalance.³³

Increased awareness of the high prevalence of metabolic bone disease in children with long-term PN dependency requires monitoring, including regular measurement of serum alkaline phosphatase, Ca, PO₄, Mg and vitamin D, urine Ca and PO₄ concentrations and bone mineral density. Studies exploring parenteral Ca and PO₄ requirements have been published in the past. The new guideline endorses higher requirements of Ca and PO₄ (Ca 0.8–1.5 mmol/kg/day and PO₄ 0.7–1.3 mmol/kg/day).

VITAMINS

Vitamins are added to lipid emulsion and no changes have been made to recommended doses.³⁵ Parenteral requirements of vitamin A are still debated, but its importance is confirmed by new studies suggesting that it decreases the incidence of retinopathy of prematurity and reduces oxygen requirement and deaths. The proposed dose for preterm babies is 700–1500 IU/kg/day (227–455 ug/kg/day) with no change in the dose for other groups (150–300 ug/kg/day term infants, 150 ug/day older children).³⁵ In the preterm, the new recommendation for vitamin D is increased from 30 to 80–400 IU/kg/day (or 200–1000 IU/day) in order to maintain a serum concentration of >50 nmol/L. The recommended dose for infants has increased from 32 to 40–150 IU/kg/day (or 400 IU/day) and to 400–600 IU/day in older children.

SMOF emulsion contain higher concentrations of vitamin E³⁶; the recommended dose of vitamin E for children aged <11 years has increased from 7 to 11 mg/day. The dose for preterm infants and infants <12 months remains the same at 2.8–3.5 mg/kg/day with a maximum of 11 mg/day. The recommended dose

for vitamin K remains unchanged, at 10 ug/kg/day in preterm and term infants up to 1 year and 200 ug/day in older children. Undercarboxylated serum vitamin K-dependent proteins (PIVKA-II) assay is advocated as a biomarker of subclinical vitamin K deficiency.³⁷ No changes have been made for water soluble vitamins (B, C, niacin, pantothenic acid, biotin, folic acid) except for pantothenic acid (vitamin B5) in preterm infants and infants up to 12 months of age, based on expert opinion and increased from 1 to 2 to 2.5 mg/kg/day.

VENOUS ACCESS

One of the major changes related to venous access is with regard to CVC 'locks' and flushes. Use of antibiotic line locks alone to treat CVC infection is not endorsed.³⁸ Ethanol lock has been shown to confer benefit when used to prevent CVC infection, but only in observational studies.³⁹ Taurolidine, however, is a very effective antiseptic against Gram negative and positive bacteria as well as fungi. There is now a strong recommendation to use it for line locks to prevent infections based on a number of studies including a randomised cross-over trial in adults.⁴⁰ There is no evidence that organisms can develop resistance. An old case-control study showed possible benefit in giving prophylactic antibiotics at the time of CVC insertion, but a recent systematic review⁴¹ invalidated that finding and preinsertion antibiotics are not recommended. There is a little scientific evidence relating to where the CVC tip should be positioned in infants and small children in order to minimise risk of complications. In the case of femoral catheters, the tip should be positioned above the entry points of the renal veins (mainly above the first lumbar vertebra).³⁸ There is no benefit in using heparin to prevent CVC occlusion in a catheter being used regularly; this does not apply to neonatal CVC or to CVC in children when being accessed intermittently. A strong recommendation is made to use recombinant tissue plasminogen activator or urokinase for unblocking catheters.⁴² The 2005 guideline recommendation for skin disinfection using 2% chlorhexidine has been changed to a combination of 2% chlorhexidine solution in 70% isopropyl alcohol before and after CVC insertion,⁴³ but not in infants younger than 2 months old.

ORGANISATION OF PN

The key importance of a multidisciplinary nutritional support team for PN patients is confirmed in recent studies. Previous studies pointed to the benefit of protecting PN fluids from light to prevent the generation of oxidants. A recent meta-analysis of trials in preterm infants found a reduction in mortality of up to 50% in the light-protected groups.⁴⁴ Effective means of providing photoprotection now need to be developed, and the utility assessed in older patients on long-term PN. The effects of particulates in large volume parenterals were investigated in a randomised trial

of children receiving PN in intensive care.⁴⁵ Filters were associated with a significant reduction in overall complication rate, a reduction in systemic inflammatory response syndrome and a reduction in length of stay. There is a strong recommendation to use inline filtration for all PN fluids.

Small volume of enteral feeds should be given to PN-dependent patients whenever possible, and at the weaning stage, breast milk will be the first choice for newborns and infants. During early infancy and severe illness, elemental formula can be given in first instance, then switching to extensively hydrolysed and then to polymeric feeds. Studies are needed to evaluate the choice of enteral feed while on PN, comparing tolerance/efficacy of elemental with polymeric formula and extensively hydrolysed formula.

HOME PN (HPN)

The number of patients receiving HPN has increased by 30%–40% in recent years, and short bowel syndrome (SBS) remains the most frequent indication for HPN with a rise in incidence around 30%–40% in recent years. New insights into the pathophysiology increases every year with gut microbiota and dysbiosis now being brought into focus.⁴⁶ The role of surgical interventions in SBS continues to be controversial and its optimal timing in order to allow bowel adaptation is still unknown. Hormonal therapies including human growth hormone, the glucagon-like peptide 2 analogue teduglutide and oral insulin have shown benefit in trials but more evidence is needed. Teduglutide is hugely expensive and appears to confer marginal benefit, with modest reduction in PN dependency providing treatment is continued long term.

HPN should be considered when PN dependency is likely to be for at least 3 months and there is a favourable home environment. Using all-in-one bags and mixtures with a higher stability reduces both risks and costs. Early referral to an intestinal rehabilitation centre that can provide 24 hours support and has close links to a transplantation unit is likely to benefit long-term survival.⁴⁷

COMPLICATIONS

In the case of fungal sepsis, small case series have shown that an antifungal catheter lock can eradicate the CVC infection but more studies are needed and current practice should remain CVC removal. Extrapolated from adult series, the technique to confirm a CVC infection without catheter removal is by calculating the differential time to positive culture between blood samples drawn from the catheter and from a peripheral vein or additional lumen.⁴⁸

Peroxidation of lipid emulsions may be driven by exposure to oxygen within the bag, photodegradation, an increasing ambient temperature, the type of container used, trace elements in the formulation and the content of alpha-tocopherol within the bag. To

reduce this risk, the use of photoprotection and multi-layer bags is recommended.⁴⁸ The new lipid emulsions may improve cholestasis and ursodeoxycholic acid should also be considered for treatment.

STANDARD VERSUS INDIVIDUALISED PN PRESCRIPTION

Studies published in recent years indicate that in many situations, the newly available standard feeds can meet nutritional requirements sometimes offering a better intake of amino acids, energy, glucose and calcium and decreasing the incidence of significant electrolyte disturbances in preterm newborn.⁴⁹ In the vast majority of paediatric patients, these solutions can be used safely for short periods of time and are preferred over individualised feeds.⁵⁰ These may, however, still be required in specific cases with unusual requirements such as fluid and electrolyte imbalance or those requiring long-term PN.

CONCLUSION

Since its introduction into clinical practice 50 years ago, PN has undergone many refinements. The evidence-based review of the literature by ESPGHAN members and others promotes best practice but raises many unanswered questions and points the way forward for future research. These guidelines provide a firm foundation for clinicians concerned with providing their patients with safe and effective PN, informed by the most recent scientific data.

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