Optimising parenteral nutrition for the very preterm infant

This article reviews the relationship between neonatal parenteral nutrition (PN) and early postnatal growth failure in the very preterm infant. The implications for long-term neurodevelopmental outcome for these infants are considered. The evidence base for different neonatal PN macronutrient contents, formulations and methods of administration is explored. A new concept is proposed: standardised, concentrated neonatal parenteral nutrition, to allow consistent nutrient delivery in the early neonatal period.

Colin Morgan
MD MRCP FRCPCH
Consultant Neonatologist, Neonatal Intensive Care Unit, Liverpool Women's Foundation Trust
email: colin.morgan@lwh.nhs.uk

Keywords

preterm; very low birthweight infants; parenteral nutrition; protein; energy; growth failure; neurodevelopment

Key points

Morgan C. Optimising parenteral nutrition for the very preterm infant. *Infant* 2011; 7(2): 42-46.

1. Early postnatal growth failure is the norm for very preterm infants and is at least partly due to inadequate nutritional intake in the first four weeks.
2. Early growth failure has neurodevelopmental implications long after the nutritional insult has passed.
3. Inadequate early neonatal nutritional intake often results from a failure to prioritise nutrition in parenteral nutrition (PN) protocols and is further exacerbated by limitations in neonatal PN formulations and methods of administration.
4. A standardised, concentrated neonatal PN regimen offers a novel approach to address some of the limitations in current neonatal PN formulation and administration.

Approximately 5400 infants are born alive under 30 weeks' gestation each year in England, Wales and Northern Ireland. Not all of these infants survive: 70% of infants born before 26 weeks go home from hospital. Of the survivors at least half have significant neurocognitive disabilities[1]. Although many factors are associated with an increased risk of neurocognitive impairment, postnatal growth failure is now recognised as an important and potentially reversible risk[2]. Suboptimal growth is common in very low birthweight (VLBW) infants[3] especially in those under 26 weeks[4]. Head growth is an especially important measure of growth failure because it correlates with brain growth[5]. Hack et al showed that subnormal head size at eight months was predictive of poorer verbal and performance IQ scores at eight years[6]. Similar findings have been demonstrated in a local cohort of VLBW infants[7,8]. Brain growth by 28 days after birth and the expected date of delivery are key predictors of long-term brain growth[8].

Postnatal growth failure: causes and consequences

Early postnatal growth failure or extrauterine growth restriction describes the severe nutritional deficit that develops in preterm infants in the first few weeks of life[2]. The deficit refers to the gap between the energy and protein (and other nutrients) required to mimic fetal growth rates and the energy and protein that is actually delivered to the preterm infants. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) currently recommend a calorie intake of 120kcal/kg/day and a protein intake of 3g/kg/day. These are estimates based on matching fetal growth *in utero*[9] but do not take into account other factors that may increase individual infant requirements (such as catch-up growth, sepsis and chronic respiratory disease) and therefore increase the risk of postnatal growth failure[10]. Indeed, there is some evidence to suggest postnatal malnutrition is inevitable based on current recommendations[11]. The nutritional deficit is most marked in the first month, especially the first week after birth. It is greater in the sickest and very preterm infants. It is multifactorial in origin[3] and reflects the difficulties in feeding preterm infants.

The role of neonatal parenteral nutrition

Very preterm infants have a gut that is too immature to digest milk in sufficient quantity to meet nutritional requirements. As a consequence, virtually all preterm infants <30 weeks' gestation require parenteral nutrition (PN) for a period that depends on gestation, birthweight and other morbidities. Complete dependence on PN (>75% nutritional intake) increases from a mean of 7.4 days to 20.8 days as birthweight falls from 1200g to 600g[3] with a combined mean of 15.6 days for all infants <29 weeks[12]. However, there is a further period before full enteral feeds are established (mean 34.5 days in infants <600g).

Thus, neonatal nutrition can be divided into three phases:

1. Mainly parenteral nutrition
2. Transition from parenteral to enteral nutrition
3. Full enteral nutrition.

There are wide variations between centres in all three phases of neonatal nutritional management. Lack of consistency within individual centres may also impair neonatal nutrition[13] and addressing this issue may improve early nutritional outcomes[13,14]. However, in the smallest and very preterm infants PN dominates nutritional management and it is this group that has the highest incidence of early and late growth failure and long-term neurocognitive disability. Therefore effective PN delivery is essential to avoid major early nutritional deficits in these infants.

The importance of early protein intake

There are major differences between centres in the way neonatal PN is introduced and delivered. This usually results from anxieties about adverse metabolic complications following too rapid introduction of PN and reflects evidence from studies evaluating the earliest neonatal PN formulations[15]. Since then, PN composition (particularly amino acid formulation) has undergone considerable modification but these early studies continue to have profound effects on nutritional policies[15]. More recent evidence suggests amino acids can be rapidly introduced without metabolic complications[16-20] but many units in the UK continue to delay the introduction of protein and/or slowly phase in protein intake over the first five days (**FIGURE 1**). Early, aggressive protein introduction is essential if the high fetal protein accretion rates are to be matched and the large protein deficits, routinely encountered in the first week of life, avoided. Early positive protein balance is achievable, even in sick infants. Current recommendations[21] support amino acid intakes from 2.5-3.5g/kg/day up to a maximum of 4g/kg/day.

Protein, calories and PN

Increasing protein without adequate energy (and vice versa) will result in ineffective protein utilisation. While optimal energy protein ratios in the preterm infant are controversial, it is accepted that a minimum of 20-25kcal/g protein is required[15,22]. Early intolerance of both glucose and lipid infusions can impair early energy intake. Increased protein administration is more effective at increasing protein deposition than increased calorie intake once energy intake exceeds 50-60kcal/kg/day[15]. However, in preterm infants 100-120kcal/kg/day are recommended for maximal protein accretion[23] and these projections are supported by recent evidence[24] evaluating different amino acid dosages.

The maximal non-protein energy intake in a PN regimen will be determined by the lipid and glucose intake. Glucose intakes that start at 6-12g/kg/day and are gradually increased to a maximum of 18g/kg/day are currently recommended[21]. Hyperglycaemia is a common complication frequently managed with insulin infusions, although the long-term risks and benefits are still unknown[21]. Although recommendations suggest lipid should also be introduced gradually (starting at 1g/kg/day and increasing to 3g/kg day) to avoid hyperlipidaemia, the evidence base is limited. Lipids can be increased to a maximum of 4g/kg/day but should not exceed 40% non-protein calorie total[21]. Although the higher intakes for glucose and lipid are designed to allow fetal growth and protein deposition rates, the optimal intakes are unknown. One recent study suggests that carbohydrate is the major determinant of optimal growth in preterm infants[25].

Early protein and calorie intake and long-term neurodevelopmental outcome

There are few studies comparing standard and maximum PN regimens but there is evidence of improved postnatal growth[26-28]. There is still less evidence that any improvements in growth affect long-term neurodevelopment. A recent study[29] investigated the effect of early introduction of amino acids on growth and development. Improvements in PN growth were seen at 36 weeks' post-conceptual age but with the exception of head circumference these did not persist until 18 months. No differences in neurodevelopment were identified at 18 months despite the reduced head growth. A recent local study[12] did not show improved growth or neurodevelopmental outcome between the groups but did not achieve the differences in nutritional intake expected. It did show a correlation between energy deficit (first 28 days) and worse neurodevelopmental outcome at three months[30]. Other recent work[31] related early nutritional intake of a cohort of extremely low birthweight survivors with 18 month neurodevelopmental outcomes (Mental Development Index, MDI). The statistical models indicated:

- 10kcal/kg/day increase in week 1 energy intake, increased 18 month MDI by 4.6 points
- 1g/kg/day increase in week 1 protein intake, increased 18 month MDI 8.2 points
- first week nutrition predicts 18% of MDI at 18 months.

While all this evidence provides a compelling association between early nutrition and later neurodevelopmental outcome, definitive randomised controlled trial evidence of causation is still lacking.

Standardised versus individualised PN

For much of the last 30 years, the received wisdom has been that the labile, unpredictable metabolic needs of the very preterm infant require sophisticated individualised PN prescription[32]. Few studies have assessed the most effective way to deliver PN in clinical practice even though there is evidence that current practice leads to significant energy and protein deficits by the fifth week of life[11]. Some of these failings reflect the limited knowledge of neonatal PN prescribers[33,34]. Computer aided prescribing has been shown to overcome some of these difficulties and can improve protein and energy intake[35,36]. As discussed earlier, many PN protocols systematically introduce a delay in establishing sufficient protein and calorie intake in the first week. This is often exacerbated by the perceived need to focus on biochemical and metabolic instability to the exclusion of nutritional priorities. In fact, the need for flexibility for the early nutritional intake of preterm infants is often exaggerated, the nutritional needs are clear and consistent, what is required is a way to prioritise and deliver them in the face of highly variable, rapidly changing fluid and electrolyte needs.

At first sight, the flexible individualised neonatal PN (iNPN) prescription would appear to be the best way to manage

rapidly changing variations in fluids and electrolytes. However, while the individualised prescription is flexible, the manufactured iNPN bag is not. It does not allow rapid responses to changes in fluid and electrolyte requirements after the bag had been prescribed. A local study[12,30] compared head growth using two iNPN regimens. Although calories and protein were increased by 30% and 33% respectively in the PN formulation for the hyperalimentation group (PN macronutrients increased above recommended levels) actual energy and protein intake (first 14 days) only improved by 11% and 16% respectively. Delivery of PN was impaired by co-administration of other drug infusions, fluid restriction and changing electrolyte requirements. The former can rarely be overcome by increasing fluid requirements and the latter may require PN to be abandoned for a short period until a new individualised prescription is available. Thus, maximising nutritional intake in very preterm infants cannot be guaranteed by simply increasing the macronutrients in the individualised PN formulation.

Effective PN delivery requires individual assessment of each infant's total fluid requirements and all additional infusions. The lower the fluid requirements and the more drug infusions, the less fluid is available to deliver PN. Moreover, the sickest infants are more likely to require multiple drug infusions and be fluid restricted. Increasing the concentration of the PN has the potential to alleviate this problem in nearly all infants but is limited by the stability of certain PN constituents at high concentrations. There have been many studies looking at the stability of adult PN formulations but none has addressed the special problems of the neonatal intensive care population or the optimal concentration of neonatal PN.

Stability issues also make it more difficult to manufacture individualised PN bags at high concentrations. This can be overcome by a standard PN solution. Again, standard PN solutions have been extensively evaluated in adults, not least because of the cost and capacity planning implications of individualised PN prescriptions for pharmacy aseptic units. As discussed earlier, the need for growth combined with the heterogeneity and clinical instability of the neonatal intensive care population has made using standard PN solutions difficult and some studies

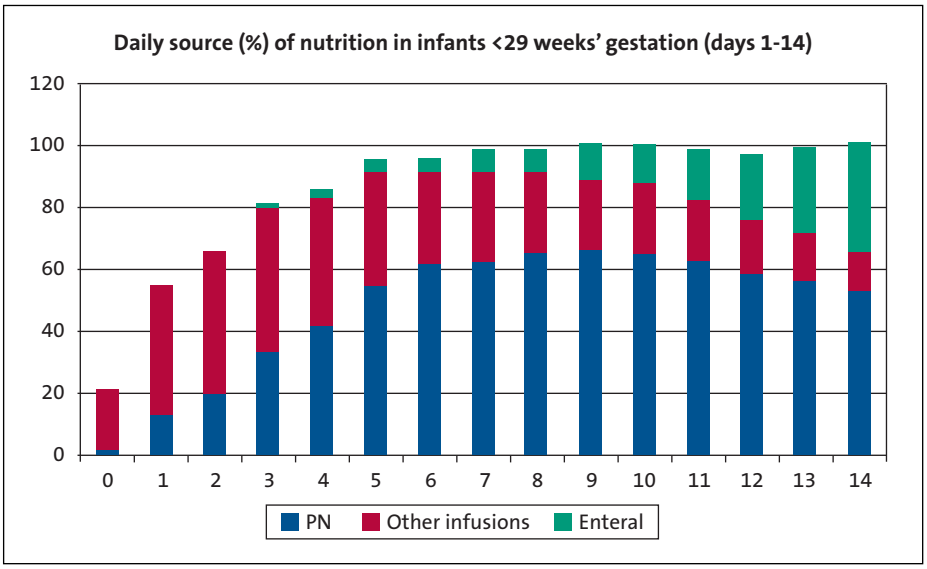

FIGURE 1 Graph to show nutritional intake over first 14 days (completed days) during original standardised concentrated neonatal PN (scNPN) regimen (unpublished audit data, 2006). In this regimen, optimal nutritional intake (100%) is achieved at 150mL/kg/day and full PN is achieved at 100mL/kg/day (67%). The other infusions include the supplementary 10% dextrose infusion as well as drug/electrolyte infusions (mostly in 10% dextrose). This graph demonstrates how the PN nutritional 'compartment' is protected by supplementary dextrose 'compartment' that can be reduced to allow for additional drug infusions without reducing PN. However, it also shows how the gradual introduction of scNPN (based on the contemporary protocol) delays full PN until day 6. This is explains how many PN protocols at the time (and many still in current use) impair early protein intake and why the scNPN regimen did not improve protein intake in the first seven days (see **Table 1**). The scNPN regimen has since been modified to address this issue.

continue to emphasise this[36,37]. However, increasingly evidence suggests that with careful attention to local workload, formulation and PN prescribing practice most infants can be managed on a standard PN formulation[38-43]. Most of the difficulties with standardised PN prescriptions relate to huge individual variations in electrolyte (especially sodium) requirements rather than nutrients. A standardised PN solution that allows some flexibility with electrolytes can overcome this problem[39]. Alternatively (or additionally) a standardised PN regimen can include more than one standardised formulation. A standardised PN regimen can be customised with a sequence of formulations tailor made to the typical needs of the very preterm infant over the first two to three weeks of life[43].

Standardised concentrated neonatal parenteral nutrition

Given the lack of evidence, it is perhaps unsurprising that a recent NCEPOD review of UK neonatal PN exposed large variations in practice and quality[44]. However, some of the failings identified in the report were not due to lack of evidence. Starting neonatal PN was delayed both because the need went unrecognised (28%) or was not acted upon (17%). Early PN was deemed inadequate in more than a third of infants and inadequate monitoring was identified in nearly a fifth. The lack of an adequate local infrastructure to support neonatal PN usage is a recurrent theme. Nevertheless, while it is recognised that considerable improvements could be made simply by setting national standards and guidance, it is also very clear there is a lack of good randomised controlled trials evaluating all aspects of neonatal PN. This work needs to combine nutritional research with evaluation of all the practicalities associated with neonatal PN manufacture and administration.

The fundamental problem is that neonatal PN has to balance two competing priorities:

- Extreme flexibility for fluid and electrolyte management
- Consistent optimal nutritional delivery.

Both can be accommodated in a 'two compartment' model. Such a model, comprising a relatively inflexible (protected) nutrition compartment (maximum 100mL/kg/day) and a highly flexible supplementary fluid compartment (usually 50mL/kg/day), has been developed

in the author's unit. To deliver this system a concentrated PN regimen (with standard macronutrient content) was developed (aqueous PN in 85mL/kg/day); using standardised concentrated PN (scNPN) bags. Together with the separate lipid component (maximum 15mLl/kg/day) this comprised the nutrition compartment. The supplementary fluid compartment (approximately 50mL/kg/day but highly variable if necessary) consisted of 10% dextrose. This compartment is then reduced or increased as total fluid requirements demand. Unexpected electrolyte derangement is corrected using standardised electrolyte infusions that replace part of the supplementary infusion as required. All standardised drug infusions are managed in the same way. Changes in infusion rate are titrated against the supplementary infusion not the nutrition compartment. Finally, early introduction of enteral feeds results in the reduction of the supplementary infusion until the enteral feed rate exceeds the supplementary infusion rate. Only then is PN reduced. This system allows maximum flexibility of fluid, electrolyte and drug infusion management with minimal impact on nutrient delivery.

The scNPN system of PN delivery was introduced in June 2006 at the Liverpool Women's Hospital (LWH) and underwent extensive audit to evaluate the effectiveness of PN delivery[43]. The actual protein and calorie intakes were compared with the control group of the previous study using a nutritionally identical iNPN formulation[12]. This study demonstrated that the median (range) percentage of target scNPN volume received by infants <29 weeks' gestation was 98.3 (80.5-102.2)%. Only three infants received <90% of the target scNPN volume with no infant receiving <80%. The eight infants receiving <95% scNPN did so because of extreme fluid restriction, severe hypoglycaemia or loss of intravenous access rather than failures of PN administration. In 12,500 hours of fluid/drug infusion data only three significant administration errors (affecting >10mL/kg/day total fluids) were identified.

This increased effectiveness of scNPN delivery also resulted in improved protein intake (**TABLE 1**) even though the protein content of iNPN and scNPN were identical (3g/kg/day). This was only apparent after the first week because the phased increase in both PN regimens does not deliver maximal PN until day 6-7 (**FIGURE 1**). The mean (SD) daily protein intake during days 7-14 (after maximal scNPN achieved) was 3.2 (0.4) g/kg/day and non-protein calories 91.0 (12.4) kcal/kg/day. A further important finding (although not part of the original study design) was that mean protein intake: 32.6 (±3.6) g/kg/14days in the hyperalimentation (prescribed 4g/kg/day protein) group of the previous RCT[12] was also exceeded by the scNPN formulation ($p<0.02$).

	iNPN (n=59)	scNPN (n=38)	P value
Protein take (g/kg/7days)	11.9 (1.3)	12.0 (1.9)	0.78
Protein take (g/kg/14days)	28.1 (2.5)	34.4 (3.5)	<0.001
Calorie take (kcal/kg/7days)	505 (48)	488 (54)	0.12
Calorie take (kcal/kg/14days)	1159 (96)	1208 (125)	0.04

TABLE 1 Comparison between iNPN and scNPN groups[43]. Comparison of early protein and calorie intakes in infants (<29 weeks' gestation) receiving an individualised neonatal parenteral nutrition (iNPN) regimen and a standardised concentrated neonatal parenteral nutrition (scNPN) regimen.

The annual cost saving following the introduction of scNPN was £39,510, a reduction of 38% when compared to the previous iNPN regimen. This does not include the costs of additional consumables (syringe and giving sets), capital equipment use (extra infusion pumps) and nursing time (making standardised electrolyte infusions) incurred by the scNPN regimen. However, some consumable costs are reduced by the scNPN regimen and nursing time could be greatly reduced by including standardised electrolyte solutions in the aseptic unit manufacturing process.

These findings also showed how PN protocols impair protein delivery in the first week of life (**FIGURE 1**). The unit PN protocol has now been changed, in response to the evidence described earlier, to introduce protein at 1.5-2g/kg/day within two hours of birth rather than a slow introduction over five days (typical of most protocols at the time). The scNPN regimen is designed to 'protect' this early nutrition from other competing needs within the total intravenous fluid volume (eg inotropic support). This will ensure that actual protein delivered matches the protein prescribed in the first week of life allowing the full benefits of scNPN regimen from birth.

Although central and peripheral line complication rates for scNPN were not formally assessed in the initial study[43], there has been no evidence of increased extravasation injuries with the new formulation (in fact there has been a fall, probably due to decreased peripheral PN usage). Although the aqueous scNPN bag has a higher osmolality than many PN solutions (approximately 1200mosmol/L) this is effectively diluted by coadministration of supplementary dextrose and lipid. With more than four years' experience of the scNPN regimen, it now appears peripheral use is also well tolerated although the same precautions apply to peripheral infusions as with any other hyperosmolar solutions and our recommendation is to only use peripheral PN for short periods.

The SCAMP nutrition study

Having implemented an aggressive early nutritional strategy and demonstrated the efficiency of the scNPN regimen, the next step is to increase the macronutrient content of the scNPN formulation even further to approach the levels described at the upper limits of current recommendations[26]. This new formulation of scNPN ($scNPN_{max}$) contains approximately 30% more protein and calories. It is currently the subject of a single centre, partially blinded, randomised controlled trial using the original scNPN formulation as the control group: the Standardised, Concentrated, Additional Macronutrients in Parenteral (SCAMP) Nutrition Study (EudraCT number 2008-008899-14; ISRCTN 76597892).

The SCAMP nutrition study is recruiting infants at 24^{+0} to 28^{+6} weeks' gestation and <1200g. Infants are randomised (following parental consent) at 48-120 hours of age to receive either scNPN (control) or $scNPN_{max}$ (intervention). The primary outcome for the SCAMP nutrition study is head growth at 28 days. The secondary outcomes include a more detailed neurodevelopmental evaluation: head growth modelling in the first 28 days and

up to 36 weeks corrected gestational age (CGA), brain MRI at 40-42 weeks (CGA) and neurodevelopmental assessment (Bayley III) at 18 months CGA. The secondary outcomes also include a full range of biochemical, metabolic and infective markers of scNPN tolerance and complications. Health economics form an important part of the assessment given the potential savings from a standardised regimen. This includes detailed evaluation of nutritional intake (including efficiency) as well as mathematical modeling to allow comparison with a theoretical individualised PN regimen. This ensures that the SCAMP nutrition study addresses questions of patient safety and economic viability required for any future wider implementation programme, as well as the important scientific questions relating to neurodevelopmental outcome.

References

1. **Wood N.S., Marlow N. Costeloe K. et al.** Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. **Clarke R.H., Wagner C.L., Merritt R.J. et al.** Nutrition in the intensive care unit: how do we reduce the incidence of extrauterine growth restriction? *J Perinatol* 2003;23:337-44.
3. **Ehrenkranz R.A., Younes N. Lemons J.A. et al.** Longitudinal growth of hospitalized very low birthweight infants. *Pediatrics* 1999;104:280-89.
4. **Wood N.S., Costeloe K., Gibson A.T. et al.** The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F492-500.
5. **Cooke R.W., Lucas A., Yudkin P.L. et al.** Head circumference as an index of brain weight in the fetus and newborn. *Early Hum Dev* 1977;1:145-49.
6. **Hack M, Breslau N, Weissman B et al.** Effect of very low birthweight and subnormal head size on cognitive abilities at school age. *N Engl J Med* 1991;325:231-37.
7. **Cooke R.W., Foulder-Hughes L.** Growth impairment in the very preterm and cognitive and motor performance at 7 years. *Arch Dis Child* 2003;88:482-87.
8. **Cooke R.W.** Are there critical periods for brain growth in children born preterm? *Arch Dis Child Fetal Neonatal Ed* 2006;91:F17-20.
9. **Cooke R.J.** Postnatal growth in preterm infants. In: *Neonatal Nutrition and Metabolism.* Thureen PJ, Hay WW, eds. Cambridge: Cambridge University Press; 2006:pp47-57.
10. **Berry M.A., Abrahamowicz M., Usher R.H.** Factors associated with growth of extremely premature infants during initial hospitalisation *Pediatrics* 1997;100:640-46.
11. **Embleton N.E., Pang N., Cooke R.J.** Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics* 2001;107:270-73.
12. **Tan M.J., Cooke R.W.I.** Improving head growth in very preterm infants – a randomized controlled trial I: neonatal outcomes. *Arch Dis Child* 2008;93: F337-41.
13. **Olsen I.E., Richardson D.K., Schmid C.H. et al.** Intersite differences in weight growth velocity of extremely premature infants. *Pediatrics* 2002;110:1121-32.
14. **Bloom B.T., Mulligan J., Arnold C.** Improving growth of very low birth weight infants in the first 28 days. *Pediatrics* 2003;112:8-14.
15. **te Braake F.W.J., van den Aaker C.H.P., Riedijk M.A. et al.** Parenteral amino acid and energy administration to premature infants in early life. *Sem Fetal Neonatal Med* 2007;12:11-18.
16. **te Braake F.W.J., van den Aaker C.H.P., Wattimena J.L. et al.** Amino acid administration to preterm infants directly after birth. *J Pediatr* 2005;147: 457-61.
17. **Murdock N., Crighton A., Nelson L.M.** Low birthweight infants and parenteral nutrition immediately after birth. II Randomised study of biochemical tolerance of intravenous glucose, amino acids and lipid. *Arch Dis Child Fetal Neonatal* Ed 1995;73:F8-12.
18. **Thureen P.J., Melara D., Fennessey P.V. et al.** Effect of high versus low amino acid intake on very low birth weight infants in the early neonatal period. *Pediatr Res* 2003;53:24-32.
19. **Ibrahim H.M., Jeroudi M.A., Baler R.J. et al.** Aggressive early total parenteral nutrition in low-birth-weight infants. *J Perinatol* 2004;24:482-86.
20. **Kotsopoulos K., Benadiba-Torch A., Cuddy A.** Safety and efficacy of early amino acids in preterm <28 weeks gestation: prospective observational comparison. *J Perinatol* 2006;12:749-54.
21. **Koletko B., Goulet O., Hunt J. et al.** 1. Guidelines 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 Society for Paediatric Research (ESPR). *J Paediatr Gastroentrol Nutr* 2005;41(Suppl 2):S1-87.
22. **Kashyap S., Schulze K.F.** Energy requirements and protein energy metabolism and balance in preterm and term infants. In: *Neonatal Nutrition and Metabolism.* Thureen P.J., Hay W.W., eds. Cambridge: Cambridge University Press; 2006:pp134-46.
23. **Thureen P.J., Hay W.W.** Intravenous nutrition and postnatal growth of the micropremie. *Clin Perinatol* 2000;27:197-219.
24. **Clark R.H., Chace D.H., Sptizer A.R.** Effects of two different doses of amino acid s supplementation on growth and blood amino acid levels in premature infants admitted to the neonatal intensive care unit: a randomized controlled trial. *Pediatrics* 2007;120:1286-96.
25. **Collins C.T., Gibson R.A., Miller J. et al.** Carbohydrate intake is the main determinant of growth in infants born <33weeks gestation when protein is adequate. *Nutrition* 2008;24:451-57.
26. **Wilson D.C., Cairns P., Halliday H.L. et al.** Randomised controlled trial of an aggressive nutrition regimen in sick very low birthweight infants. *Arch Dis Child* 1997;77:F4-F11.
27. **Porcelli P.J., Sisk P.M.** Increased parenteral amino acid administration to extremely low-birth-weight infants during early postnatal life. *J Pediatr Gastroenterol Nutr* 2002;34:174-79.
28. **Dinerstein A., Nieto R.M., Solana C.L. et al.** Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth-weight infants. *J Perinatol* 2006;26: 436-42.
29. **Poindexter B.B., Langer J.C., Dusick A.M. et al.** Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevlopmental outcome. *J Pediatr* 2006;148:291-94.
30. **Tan M.J., Cooke R.W.I.** Improving head growth in very preterm infants – a randomized controlled trial II: MRI and developmental outcomes in the first year. *Arch Dis Child Fetal Neonatal Ed* 2008;93: F342-46.
31. **Stephens B.E., Walden R.V., Gargus R.A. et al.** First week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* 2009;123:1377-43.
32. **Riskin A., Shiff Y., Shamir R.** Parenteral nutrition in neonatology - to standardize or individualize? *IMAJ* 2006;8:641-45.
33. **Ahmed M., Irwin S., Tuthill D.P.** Education and evidence are needed to improve neonatal parenteral nutrition practice. *J Parenter Enteral Nutr* 2004;28:176-79.
34. **Grover A., Khashu M., Mukherjee A. et al.** Iatrogenic malnutrition in neonatal intensive care units: urgent need to modify practice. *J Parenter Enteral Nutr* 2008;32:140-44.
35. **Puago M.A., Nguyen H.L., Sheridan M.J.** Computerized PN ordering optimizes timely nutrition therapy in a neonatal intensive care unit. *J Am Diet Assoc* 1997;97:23-29.
36. **Eleni-dit-Trolli S., Kermorvant-Duchemin E., Huon C.** Early individualized parenteral nutrition for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F152-53.
37. **Smolkin T., Diab G., Shohat I. et al.** Standardized versus individualized parenteral nutrition in very low birth weight infants: a comparative study *Neonatology* 2010;98:170-78.
38. **Beecroft C., Martin H., Puntis J.W.** How often to parenteral nutrition prescription for the newborn need to be individualised? *Clin Nutr* 1999;18:83-85.
39. **Keady S., Morgan C., Ozzard A., Chauhan B.** Effect of a standard neonatal aqueous parenteral nutrition formulation on aseptic unit capacity planning. *Eur e-J Clin Nutr Metab* 2010;5:e14-e17.
40. **Yeung M.Y., Smyth J.P., Maheshwari R. et al.** Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation. *J Paediatr Child Health* 2003;39:631-37.
41. **Lenclen R., Crauste-Manciet S., Narcy P. et al.** Assessment of implementation of a standardized parenteral nutrition formulation for early nutritional support of very preterm infants. *Eur J Pediatr* 2006;165:512-18.
42. **Skouroliakou M., Koutri K., Stathopoulou M. et al.** Comparison of two types of TPN prescription methods in preterm neonates. *Pharm World Sci* 2009;31:202-08.
43. **Morgan C., Badhawi I., Grime C., Herwitker S.** Improving early protein intake in very preterm infants using a standardised concentrated neonatal parenteral nutrition formulation. *Eur e-J Clin Nutr Metab* 2009;4:e324-e328.
44. **Mason D.G., Puntis J.W., McCormick K., Smith N**. Parenteral nutrition for neonates and children: a mixed bag. *Arch Dis Child* 2010; doi:10.1136/adc.2010.188557.