An update on neonatal parenteral nutrition

Parenteral nutrition (PN) – the provision of nutrients by an intravenous route – can be used as the sole source of protein, lipid, carbohydrate and other essential nutrients (total PN, TPN) or to supplement milk feeding (partial PN). PN is available in almost all neonatal units in the UK although there is much variation in practice. This article reviews the recent British Association of Perinatal Medicine framework for practice on the provision of PN and emphasises the importance of developing local guidelines to ensure consistency of practice.

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Key points

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1. PN is an essential component of the care of sick and preterm infants but is not without risk.
2. The recent BAPM framework for practice describes minimum standards for the nutrient content of neonatal PN and makes recommendations for prescribing, administering and monitoring PN in neonatal units (NNUs).
3. The framework for practice should enable all NNUs to develop local guidelines for safe and effective delivery of PN.

Since the first report in 1968 of a term baby successfully managed with TPN,[1] enormous progress has been made both with regard to optimising the nutritional content of PN, and in the design and manufacture of delivery systems. In 2008 reports from both the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) and the Paediatric Chief Pharmacist's Group highlighted many deficiencies in the provision of PN to neonates in England, Wales and Northern Ireland, with only 23.5% receiving PN care considered to represent good practice.[2,3] The documents reported issues in prescribing and administration of neonatal PN and highlighted differing practice between units, particularly for the smallest (and potentially most vulnerable) babies.

In response to these documents, the British Association of Perinatal Medicine (BAPM) recently published *The Provision of Parenteral Nutrition within Neonatal Services: A Framework for Practice*.[4] The framework for practice was written by a working group consisting of neonatologists, a paediatric gastroenterologist, a specialist neonatal dietician and a specialist pharmacist and was refined following feedback from BAPM members and other interested parties. The group considered the latest international consensus on neonatal nutrition from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN)[5] as well as more recently published data, and also reviewed available evidence regarding safe delivery of PN solutions. The framework for practice makes practical recommendations for prescription, administration and monitoring of PN in neonatal units (NNUs), and describes minimum standards for the nutrient content of neonatal PN, as well as those infants for whom PN should be a standard of care. The anticipation is that this new BAPM document will help networks and local NNUs to develop safe and effective guidelines for the administration of PN to infants in their care.

The rationale for neonatal PN

Extremely low birth weight (ELBW) infants are born with sufficient energy reserves for only the first 2-3 days of life and even well-grown term infants will rapidly become catabolic if not supplied with adequate protein and calories. Early weight gain is commonly suboptimal in preterm infants and this has been associated with a significant cumulative nutritional deficit and poorer neurocognitive outcome.[6,7] There is evidence that improved early nutrition leads to better outcomes and therefore healthcare professionals should always be mindful of nutrition for the babies in their care and aim to provide timely and appropriate PN when milk feeding is not possible.

Who should receive neonatal PN and when?

All infants born before 30 completed weeks' gestation and/or weighing <1,250g

at birth should be commenced on PN as soon as practical, and certainly within the first few hours of life (**TABLE 1**). Additionally, any infant who has failed (or is predicted to fail) to tolerate ≥100mL/kg/day of milk by day 5 or who subsequently cannot tolerate enteral nutrition over a significant period should be considered for PN. All NNUs caring for babies meeting these criteria should have 24-hour access to PN solutions.

Absolute indications	Gestational age <30 completed weeks (ie up to and including 29 weeks and 6 days) Birth weight <1,250g Failure to establish enteral nutrition* by day 5 of life, regardless of gestation or birth weight Inability to tolerate enteral nutrition for a period likely to result in a significant nutritional deficit**
Relative indication	Any baby ≥30 weeks' gestation considered unlikely to establish enteral nutrition by day 5.

TABLE 1 Indications for PN in neonates (BAPM, 2016).[4]
*Enteral nutrition is defined as ≥100mL/kg/day of milk. **The likelihood of a significant nutritional deficit depends on many factors including age, gestation and birth weight. PN should be considered for any baby ≥5 days of age who becomes unable to tolerate enteral feeds for ≥24 hours.

What to give?

Neonatal PN needs to supply energy, protein, essential fatty acids, minerals, electrolytes and vitamins.[7] Energy is provided as carbohydrate and lipid, commonly a combination of 10-15% dextrose and 20% lipid emulsion, respectively. A relatively stable ELBW infant has a total daily energy requirement of 100-120kcal/kg, comparable to that of a Tour de France cyclist! It would take approximately 300mL/kg/day of 10% dextrose to supply such a high calorie load and so more calorie-dense lipid emulsion is critical in providing enough energy for the baby to grow.

Most neonates will receive total PN (TPN) as a combined dextrose and amino acid (AA) solution with a separate infusion of lipid. Dextrose/AA solutions also contain electrolytes, phosphate, calcium and trace elements; they have a relatively long shelf life and should be available to be commenced immediately, normally after an umbilical or central venous line has been sited. Depending on local policy, PN may also be administered peripherally. Some NNUs use concentrated PN solutions – these are given in set daily volumes with additional clear fluids adjusted as required to maintain fluid and electrolyte balance. Concentrated PN has the advantage of making it easier to ensure that the baby receives the prescribed nutrient intake, but the disadvantage of requiring more complex fluid prescriptions with greater risk of error. Concentrated PN solutions cannot be given via peripheral veins. Rapid changes in both intracellular and extracellular fluid compartments, particularly for the smallest babies in the first few days of life, can present challenges in fluid management, but the aim should be to optimise nutrition whenever possible.

Fluid and electrolytes

It is reasonable to start on day 1 with fluid volumes of 60-100mL/kg/day, increased according to the infant's clinical condition. Measured fluid balance is unreliable and daily weighing, particularly for the smallest and sickest babies, essential. Small amounts of sodium may safely be given in the first two days (it is not possible to add phosphate to PN fluids without some accompanying sodium); daily sodium requirements will increase to at least 1-3mmol/kg following the immediate postnatal physiological diuresis. The smallest preterm infants are likely to have much higher sodium requirements due to excessive urinary losses. Similarly, potassium requirements will be highest in preterm infants, particularly those with gut pathology or who are receiving diuretic therapy.

Energy

A preterm baby needs calories to provide for resting energy expenditure as well as growth and in the absence of any milk feeds PN should provide a total of 100-120kcal/kg/day. To allow the protein in PN to be used for new tissue formation and/or tissue repair, the majority of energy provision should be from carbohydrate and lipid.

Carbohydrate

D-glucose (dextrose) is the main carbohydrate and energy source in neonatal PN and provides 3.4kcal/g. This equates to 34kcal/100mL of 10% dextrose solution. The recommended glucose intake in the neonatal period ranges from 5.8-17.3g/kg/day (4-12mg/kg/min) regardless of gestation, but preterm infants tend to have higher glucose requirements than term babies. While it is important to provide enough glucose for energy and for the utilisation of protein, too much glucose may be associated with excess fat gain and/or hyperglycaemia. Hyperglycaemia is commonly defined as a plasma glucose concentration >8.3mmol/L but most units will not consider treating hyperglycaemia unless the plasma glucose is consistently >10 or 12mmol/L. There is no good evidence to show whether tolerating hyperglycaemia (assuming that the baby is neither dehydrated nor acidotic) or reducing the blood glucose (by either reducing the infused amount of glucose or giving insulin) is better.[8] Early provision of protein helps to normalise blood sugar and high dose lipid may make things worse. It should not be forgotten that reducing the amount of glucose will necessarily reduce the baby's caloric intake, and thus adversely impact upon nutrition.

Protein/amino acids

Protein is provided in PN in the form of AAs. The available combinations of AAs for neonatal PN are designed to be as close as possible to umbilical cord blood or human milk, but there are limitations due to solubility and stability. The neonate requires at least 1.5g/kg/day protein to prevent loss of existing tissue protein, but there is a paucity of evidence regarding optimal protein intake, particularly in more mature preterm and term infants. Consensus opinion is that preterm infants meeting at least one criterion for PN at birth should be started on protein as soon as possible at a dose of 2-2.5g/kg/day, increasing towards a target protein intake of 2.7-4g/kg/day by day 5 of life. Term babies should normally only need a maximum of 3g/kg/day of protein. The ratio of energy:protein in PN influences utilisation of protein as well as optimal body composition, and it is likely that between 18-25 non-protein kcal are required per gram of protein.[5] The target

dose of protein agreed in local guidelines should be achieved by day 5 in order to minimise the early protein deficit.

Observational studies have associated higher early protein and energy intake with improved developmental outcome at 18 months, but data are limited. One study showed improved early head growth with increased protein and energy intake in very preterm infants[9] but in a similarly sized study, increased AA provision without increased energy intake was associated with poorer head growth.[10] To date there has been no randomised controlled study of neonatal PN that has reported on longer-term developmental or (perhaps just as importantly) metabolic outcomes; bigger may not always be better.

Lipid

As well as fat and calories for growth, intravenous lipids provide essential fatty acids for brain development. The fetal requirement for fatty acids increases during the third trimester from approximately 1.0g/kg/day to just over 2.0g/kg/day at term.[7] Twenty per cent lipid emulsion provides 2kcal/mL, more than five times the calorie density of 10% glucose and AA solutions and is the preparation of choice. Lipid should be given in addition to aqueous PN in a dose of 2g/kg/day on the first day of life and increased daily to a maximum of 3.5-4g/kg/day. It should be continuously infused over 24 hours. Intravenous lipid is generally well tolerated from birth even in ELBW infants; historical concerns regarding lipid toxicity have not been proven. Any potential risks of intravenous lipid are outweighed by the benefits of early provision of essential fatty acids, particularly for the smallest babies. Plasma triglyceride concentration is generally used to monitor lipid tolerance, but there is little evidence to define normal plasma triglyceride concentrations in the newborn; concentrations ≤3mmol/L are probably acceptable. Newer lipid formulations include medium chain triglycerides, olive oil and fish oils as well as soybean oil (SMOF); these may be beneficial in babies with liver disease but there are no long-term data.[11]

Micronutrients

Calcium and phosphate are required for bone structure as well as muscle and nerve function and should be provided in PN from day 1. Recommendations for phosphate intake have recently been revised upwards, and a reasonable initial dose for all neonates requiring PN would be 1.5mmol/kg/day each of calcium and phosphate. Extremely preterm babies are likely subsequently to require more phosphate. Care must be taken with adjustment of calcium and phosphate levels in PN solutions as there is potential for precipitation of salts.

Both trace elements and vitamins are nutritionally essential, but the precise requirements in the neonate remain uncertain and may vary according to gestation. The addition of trace elements reduces the stability of standard PN bags and so trace elements are generally added in the pharmacy department at the first routine PN fluid change. Similarly, intravenous vitamins must be added to PN fluids under aseptic conditions. Water soluble as well as fat soluble vitamins should ideally be given in the lipid phase of PN and commenced within 48 hours of birth. Some NNUs may choose to use a ready mixed lipid and vitamin preparation, based on convenience, safety and cost, but this is licensed only to a maximum dose of 3g/kg/day of lipid.

Practical considerations

PN is expensive and carries significant risks including toxicity, metabolic disturbance and line-associated sepsis. Safe prescription, preparation and administration of neonatal PN requires a multidisciplinary team including medical and nursing staff, pharmacists and dietitians. Local guidelines should be in place and all NNUs should undertake regular audit of practice, including whether targeted nutritional intake is achieved. All staff dealing with neonatal PN must be properly trained.

Prescription

Prescription of PN must only be undertaken by suitably trained persons and should be reviewed daily. PN and total fluids are prescribed until the baby has exceeded its birth weight; if there is significant oedema an agreed working weight should be used. Both standardised prescription charts and electronic prescribing reduce the likelihood of error. Great care should be taken in checking and documenting any changes to the prescribed infusion rate.

Preparation

PN must always be prepared in a pharmacy aseptic unit. Changes to PN at ward level risk contamination and/or problems with incompatibility of additives and must not be made. PN solutions should be stored in a fridge when not in use and allowed to reach room temperature before administration. This allows the solution to de-gas, reducing the likelihood of bubble formation. Drugs should not be added to PN solutions. Heparin affects lipid bonds and has not been shown to increase catheter patency so is not recommended.

A majority of units now use standardised, rather than bespoke (or individualised), PN solutions. Standardised PN solutions can be available 24 hours a day, are associated with lower risk of compounding and prescribing error and will be suitable for a vast majority of neonatal patients. Bespoke PN solutions should only be prescribed by an experienced clinician in conjunction with a specialist neonatal pharmacist and ideally a specialist neonatal dietitian.

Administration

The risk of extravasation injury with PN is increased due to many factors, including pH and tonicity. PN is also an independent risk factor for neonatal sepsis and catheter-associated bloodstream infection. Cost is an important factor which is added to by filters and dedicated line sets. Wastage should be kept to a minimum.

Ideally PN should be administered via a central line, particularly if the baby is expected to require PN for more than a few days. Careful attention must be paid to maintaining sterility of central lines, and local protocols for insertion and management of central lines should be in place. Central venous line position must be confirmed by X-ray before use and all staff should be aware of the possibility of line migration. Ideally a designated central line should be used exclusively for PN and not accessed for blood sampling or administration of drugs, but this may not be practical. If other infusions are to run alongside PN, care must be taken to ensure that the solutions are compatible. Some NNUs allow peripheral cannulae to be used for PN, balancing the risk of extravasation injury against the risks associated with central venous access. When using peripheral venous access, infusion of lipid via the same cannula as the aqueous component helps to protect the vein.[12] Concentrated PN solutions with high osmolarity will not be suitable for

peripheral infusion and should be labelled accordingly.

When commencing PN solutions, priming of lines and giving sets should be done under full aseptic conditions. A final safety check at the point of administration of PN should be performed, including checking the labels of PN solutions against the request form for:

- name of patient and identifying number
- route of administration (central or peripheral)
- date for infusion, expiry date and appearance of the PN solution(s).

The use of filters to reduce the risk of contamination of PN fluids is widely practised although not evidence-based.[13] There are two main intravenous filter pore sizes; the 0.22 micron filter is used for aqueous solutions and the 1.2 micron filter used for larger molecule solutions including lipid. Changing PN bags 48 hourly instead of 24 hourly does not result in increased central line-associated bloodstream infection in term and larger preterm infants.[14]

Exposure of PN solutions to light creates oxidant stress, increases degradation of vitamins and has been implicated in both impaired lipid tolerance and slower advancement of enteral nutrition. Although there is no evidence that shielding of PN solutions from light improves outcome, the practice is commonplace.[15]

Monitoring

Routine biochemical monitoring of infants receiving PN should take into consideration the duration of PN as well as gestation and comorbidities. Monitoring will usually include urea and electrolytes, calcium and phosphate, glucose, triglycerides and liver function. Additional measurement of trace elements and fat soluble vitamins should be considered for those babies who are PN dependent for more than three weeks. It is important that biochemical results are reviewed promptly and acted upon as necessary. Unexpected biochemical instability as a consequence of PN is rare but should not be missed.

Weaning PN

Minimal enteral feeds, preferably maternal or donor breast milk, should be given in conjunction with PN wherever possible to encourage gut adaptation, as well as reduce the risk of PN-associated liver disease. Weaning of PN should be described in local feeding guidelines which are reviewed as the results of feeding trials become available. Both aqueous and lipid phases of PN should be reduced proportionally as enteral feeds increase. Additional sodium may need to be given orally as the volume of aqueous PN is decreased. PN should generally be continued until at least 75% of nutritional requirement is tolerated enterally. For preterm babies after the first few days of life, this would generally be a milk intake of at least 120mL/kg/day.

- PN is an essential component of the care of sick and preterm infants but is not without risk.
- For most stable neonates PN should provide a total of 100-120kcal/kg/day by 72 hours of age.
- Regardless of gestation, the minimum amount of glucose that should be provided in the first 24 hours is 5.8g/kg/day. The maximum glucose intake should not exceed 17.3g/kg/day.
- Preterm infants meeting at least one criterion for PN at birth should be started on protein as soon as possible at a dose of 2-2.5g/kg/day. Target parenteral protein intake should be 2.7-4g/kg/day by day 5 of life. Term infants will not normally require more than 3g/kg/day of protein.
- Intravenous lipid should be given in addition to aqueous PN at a dose of 2g/kg/day on the first day of life and increased daily to a maximum of 3.5-4 g/kg/day, depending on lipid and glucose tolerance.
- All NNUs should have agreed policies for nutrition and the provision of PN.
- All NNU staff involved in the provision of PN must be suitably trained.

TABLE 2 A summary of neonatal PN.

Audit of practice

All units administering PN should have a programme for regular audit of practice including compliance with local guidelines for administration of PN and the incidence of sepsis and catheter complications. Equally importantly, the efficiency of PN in delivering target nutrition should be regularly reviewed since actual provision of macronutrients may be considerably different from that prescribed.[16]

Summary and conclusions

The key points regarding PN are highlighted in **TABLE 2**. Neonatal PN is an essential component of neonatal care with potential to influence both short and longer term outcomes. All neonatal patients deserve equal access to PN, prescribed and administered according to carefully considered local guidelines, and all neonatal staff should be trained to facilitate this. Although administration of neonatal PN is necessarily linked with fluid balance, particularly in the first few days of life, it is important that the nutritional needs of the infant be considered independently of fluid requirements. Further research, including longer term metabolic and neurodevelopmental outcomes, is required to define the optimal content of neonatal PN.

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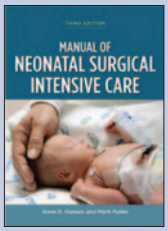
BOOK REVIEWS

Manual of Neonatal Surgical Intensive Care, third edition



Anne R. Hansen, Mark Puder
PMPH-USA, June 2016
ISBN: 9781607951940
£60.50, paperback, 738 pages

Surgical newborns are a unique patient group whose care is highly specialised, even within the fields of paediatric surgery and neonatal medicine. With improved fetal ultrasound many congenital anomalies are detected antenatally and the babies delivered in tertiary neonatal units with surgical services where they receive the majority of their inpatient care. UK surgical trainees are no longer required to work on neonatal units and may be less familiar with neonatal medicine. Yet surgical newborns still deliver in non-surgical units and surgeons need to understand principles of neonatal medicine. The *Manual of Neonatal Surgical Intensive Care*, bringing the knowledge of these two disciplines together, balances fundamental principles with practical advice to support decision making.

The book has been produced as a joint effort between the professor of surgery and director of neonatal intensive care at Boston Children's Hospital. Starting with general medical and surgical principles, including fetal medicine, it goes on to discuss specific gastrointestinal, thoracic, genitourinary, ENT (ears, nose, and throat) and neurological conditions. For each condition there is a discussion of embryology, systems for classification of anatomy, and potential surgical interventions. In addition, medical care around stabilisation, surgical intervention and longer term morbidity is discussed. Orthopaedics and managing of extravasation injuries are included but, understandably, the book doesn't cover congenital cardiac lesions. There are also useful chapters on anaesthesia and management of pain postoperatively.

The practical advice on management strategies highlights important principles of care but may conflict with local clinical guidelines.

The book will fit in a large pocket but is probably too big to carry around routinely. Its clear, diagnosis-based layout makes it an excellent quick reference guide and a basis for further reading. The *Manual of Neonatal Surgical Intensive Care* is a worthwhile text for students, nurses, doctors and surgeons caring for this fascinating group of patients.

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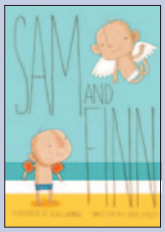
Sam and Finn



Kate Polley
The Solopreneur Publishing Company Ltd
ISBN: 9780993056918
£11.99, paperback, 31 pages
Available from: http://thestoryof-books.com/sam-and-finn

Sam and Finn is the story of author Kate Polley's twin sons. Kate wrote this book after Sam died to share his story with her surviving premature twin, Finn. It is a story of hope designed for all children and families who have experienced the loss of a twin, sibling or child.

View of a neonatal nurse. Many parents enjoy reading to their sick babies even when they are first born and in incubators. We provide a selection of books in our family room, although many parents bring their own books and keep them by the cot side to read. Over the last few years, our unit has been involved in research to try to improve understanding of the experiences of parents who have lost a baby from a multiple/twin pregnancy (the Butterfly Project – see page 222). *Sam and Finn* brings aspects of both the Butterfly Project and parent reading projects together.

This is a deeply touching and beautifully written book that expresses emotions that can be difficult to put into words. Many parents struggle to make sense of what has happened when a twin dies. They worry how they will tell the surviving twin about their brother or sister, or what they will say to other children in the family. Every parent is different so not all parents with a surviving baby on the unit may want to read this book but many will find it comforting. The names in the book can be personalised for families (information at www.personalisedchildlossbook.com).

View of a parent. When one of my twin boys died the pain was almost unbearable. I didn't know how I would cope. I was worried about my surviving boy and terrified he would also become sick. I didn't know what to say or think, or what I would say to him when he was older. I was shown the *Sam and Finn* book a few weeks after my baby died. I loved it the first time I read it, even though it made me cry. I've read it every day since then, sometimes more than once. I've ordered a personalised copy. I know it's just a children's book, but it means a lot to me.

Sister Sarah Stephenson and Jane Mackey (parent),
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