British Association of Perinatal Medicine

The Provision of Parenteral Nutrition within Neonatal Services - A Framework for Practice

Consultation comments and responses – April 2016

Consultation period: January-February 2016

Chris Jarvis **Specialist Neonatal Dietician, Nottingham University Hospitals**	
Comment	**Response**
	Executive summary: "conceived" replaced with "convened" – thank you.
Page 4: Amend "24 hour access" to "24 hour access, 7 days per week"	This has been done
Page 6: Suggested amendment: "electrolyte balance should be calculated in conjunction with plasma electrolytes"	This has been done
Page 7: Comment about energy equivalence of dextrose monohydrate – see reply to FK comment	See reply to FK comment
Page 10: Does 25 kcal/g protein refer to total or non-nitrogen calorie intake?	This is a tricky and potentially confusing issue – thank you for flagging. ESPGHAN indicate that theoretically NN calorie intake should be the range quoted as preference, but they all their recommendations as total energy. The - text has been amended accordingly, in agreement with table 2:
Are recommended protein intakes a bit high, given that parenteral requirements will be a bit lower than enteral requirements?	ESPGHAN acknowledges that the requirement for amino acids should be lower in parenterally compared to enterally fed infants, but that this may be partially offset by unpredictable absorption and metabolism of specific amino acids. Since 1g protein = approximately 1.12g AA, our choice of a recommended *protein* intake (justified to facilitate assessment of combined enteral and parenteral intake) will result in marginally more AA being supplied than ESPGHAN recommendations, but we believe that this is likely to be compensated for by variation between *prescribed* and *actually administered* intake.

Page 11: Can we omit “by 0.5 – 1 g/kg/day”, in regard to lipid increments?	Amended as suggested
Page 12: Suggestion than more soluble organic phosphate salts be used.	Amended as suggested.
Page 16: Is it practical to suggest that light shielding of giving sets be practised?	Opaque giving sets are available; the working group considers that since solutions should be protected from light, giving sets ought to comply with this, particularly for the smallest babies receiving the lowest infusion rates.
Page 17: Is the advice regarding duration of aqueous infusions consistent?	On pages 15 and 16 we present the (limited) evidence around use of inline filters. We believe that the conclusions and recommendations summarised on page 17 are consistent with the published evidence.
Page 18:	Further guidance given on minimal enteral intakes for preterm babies, as suggested.
Appendix, table 2: Do term babies need as much lipid as suggested?	The recommendation of 3-4 g/kg/day is consistent with ESPGHAN
Should we revise recommendation that no sodium be given in the first two days?	Agree – probably a little too proscriptive. Amended to “minimal”. Similarly, potassium. Consistent amendment made to page 6
Recommended PO4 starting dose less than suggested in the text.	Amended to 1.5 mmol/kg/day, to comply with 1:1 molar ratio.
Query as to whether trace element requirement is necessary	The working group believes that this information may be of interest, while noting that only standardised preparations are available.
Appendix, table 3 Monitoring table suggests measuring ferritin for babies on IV iron (inconsistent with text) Query around measuring triglycerides and albumin	Text amended to “serum ferritin” Working group acknowledge the difficulties in interpreting plasma albumin and triglycerides, but note that these measurements are common practice, and can provide some useful *guidance.* Addendum to page 17 (see under McElroy comments).
Suggested that less frequent biochemical monitoring may be appropriate for long term stable patients	Amendment as suggested

McElroy	
Comment	**Response**
Should birthweight criterion be reconsidered at <1250g or even <1500g as this fits better with the proposed gestational age limit and with information about protein loss?	Thank you – we have received similar feedback from others. Criterion changed to < 1250 g
Is there a good reason/evidence to introduce a Ca:P ratio of 1:1 when ESPHGAN suggesting 1.3-1.7?	We have suggested a Ca:P ratio of 1:1 as a *starting* dose, noting that P may subsequently require to be increased (text amended)
Lipids - it would be helpful to include a suggestion on management of elevated triglyceride levels in this section, especially as there is such varied management which inevitably leads to reduced lipid intake, and as Table 3 recommends twice weekly measurement.	There are few data to inform management of plasma triglycerides, but a general feeling that practice to date has been too cautionary. Addendum to page 17: "it is reasonable to accept (plasma triglyceride) values of up to 3 mmol/L as within normal.
Table 3. What is the evidence, or good reason, for daily LFTs? This does add a relatively fair amount of blood sampling in the extreme preterms and as a unit that does not practice this we have not seen elevated LFTs in the subsequent weeks of life.	Agree – a reasonable suggestion. Text amended

Baxter Healthcare UK	
Comment	**Response**
Page 7: The statement about glucose providing 3.4kcal/g will cause confusion. Historically the nominal value of 4kcal/g has been assigned to glucose and is used as the basis for kcal calculations for the glucose component for all licensed PN products.[1] Existing unlicensed preparations also use this value, for example East of England formulations.[2] What is the intention of adding this information? Is there an expectation that all centres will recalculate their glucose calorie intake based on the figure of 3.4kcal/g.	This anomaly has been more clearly explained in the text (page 7) After much discussion, the working group decided to retain the correct figure.
Page 12: This statement suggests that trace elements can only be added to aqueous PN, this is not a valid statement. There are reports in the literature of stable all-in-one neonatal regimens containing trace element solutions.[4] The existing licensed multi-chamber products include reference to	Thank you for this information. Amendment to page 12. Reference added.

the addition of trace element solutions.[1] Baxter Healthcare also has stability data to support the inclusion of paediatric trace element solutions in its All-in-one matrix stability matrices.[4] The inclusion of trace elements and vitamins may result in a shorter shelf life being assigned to the final product, based on the stability data that is available.	
Page 12: The reference to ready mixed lipid and fat soluble vitamins being costly infers that this is a reason not to use. If the product is licensed it would offer significant assurances over compounded products, however if unlicensed then suitable assurances should be sought in line with the NHS QA standards for outsourcing parenteral nutrition.	We agree that the current wording implies bias – amendment made: "Ready mixed lipid and fat soluble vitamin preparations are now available; a decision to use such products will need to consider convenience, safety and cost".
No mention is made of the use of filters for all-in-one neonatal solutions.	All-in-one neonatal solutions are not yet widely used and so have not been included in the Framework for Practice (with the exception of amendment to page 12)
For the first 24 hour of PN, no sodium or potassium is recommended. This is not consistent the text on page 6. Statements are made regarding the provision from 48 hours of life, however no evidence is provided to substantiate the recommendation not to supplement sodium or potassium in the first 24 hours of life, or the potential consequences of doing so. The first 24 hours of PN may not be the first 24 hours of life and therefore a standardised approach may be better facilitated if the recommendation of nil sodium/potassium on day one was revised to reflect this.	Thank you – this matter has been raised by others We trust that the amendments to page 6 and table 2 are acceptable

Lucy Stachow/David Harris **Senior Neonatal Pharmacist** **UHL NHS Trust**	
Comment	**Response**
The document looks great, clear and concise. Hopefully this will be a step forward in getting equal access to PN for all neonates nationally, and I'm	

hoping it should make it easier for regional networks to come to an agreement to use the same PN regimes for all patients in their regions rather than having disparate local practices. – thank you!	
Section: Who should receive PN and When Final para – recommends start IV glucose and AA solution ASAP after birth. No mention of fat. Later section on fat recommends to also give fat from day one, would be helpful to include similar statement after the recommendation to start AA and glucose ASAP after birth or could be misinterpreted not to start fat on day 1?	Amendment to page 6
Section:Protein and amino acids Recommendations for practice – recommendations are split between "preterm" and "Term and larger preterm" – any way to be more specific on the interpretation of preterm / larger preterm? – the reader may interpret the preterm as <30 weeks (the absolute indication for PN in Table 1) and therefore larger preterm from 30 weeks on – is this the intention as it would mean 30 weeks plus only reach 3g/kg/d protein by day 5 which seems inadequate.	Amendment to page 10
Section: Practical considerations Prescription of PN – "Any change in infusion rate……must be clearly documented on the patient's PN Rx chart". Have the membership group got any good examples of how this is achieved in practice to share? We don't currently do this, the PN is prescribed at full rate as per the labels, and the nurses are able to titrate downwards as continuous drug infusion rates or enteral intake changes or fluids are restricted (recorded and witnessed in nursing documentation but not represcribed). With sick babies on inotropes, insulin, morphine etc there can be multiple changes in the PN run rate per day – would be interesting to hear how other units get the Doctors to represcribe the PN so frequently.	The working group believes that accurate prescribing of PH is essential, but it is up to individual networks to decide how best to achieve this. Hence out with the remit of this Framework for Practice

Roberta McCarthy **Neonatal Dietician**	
Comment	**Response**

When protein is referred to, is this 'protein' or amino acids'?	We have chosen to use "protein" for ease of calculating total protein intake, once some enteral feeding has been established (see page 9)
Is there any guidance on how many days trace element free PN may be used as a main source of nutrition? I note that unsupplemented PN is allowed until trace elements can be added, but is there a specific time frame – in particular for units that cannot add trace elements on-site?	We have stated that trace elements (be) added to the first routine PN fluid change (page 12).
In the section on weaning PN, it advises 'PN should be weaned as soon as the baby is stable and considered suitable for commencement of enteral feeds' – this could mean that a baby is not yet on enteral feeds. We do not commence weaning until enteral feeds are advancing >30 ml/kg/d and I thought some centres would allow higher EN volumes before weaning PN. We also aim to maximise combined intake from PN and EN volume before titrating down PN volume.	In the absence of scientific evidence, we believe that the specifics of weaning are out with the scope of this document, and should be dictated by locally agreed policy. Text has been amended to "weaning of PN should be considered once the baby is stable and able to tolerate some enteral feeds"
Just a comment - the baseline recommended intakes for sodium and potassium in table 2 from >=72 hours (1-3 mmol/kg/d – increased as required) would be lower than we tend to get away with … Iron and vitamins are not included in the table of macro and micro-nutrients.	Already noted in text that these are minimum levels, and likely to need to be incremented, especially in the most preterm infants The text notes that iron should not be added to PN fluids within the first three weeks of life – now emphasised in table. Vitamin requirements out with the scope of this document.
Again just a comment, guidance on practice during PNALD might be useful, e.g. babies with SBS with extended PN requirement.	Out with the scope of this document. Page 11 notes that newer lipid formulations may be useful in babies with liver disease.

Zoe Lansdowne **Specialist Paediatric Pharmacist** **St Michael's Hospital** **University Hospital Bristol NHS Foundation Trust**	
Comment	**Response**
Typo on page 9 (d instead of day)	Amended, thank you
ClinOleic and SMOF max licensed doses are	Yes – text amended! (page 11)

3g/kg/day I don't know if this needs acknowledging?	
We always prescribe in mmol phosphate (page 12)	Thank you - Text changed to phosphate
SMOFvits contains both water and fat soluble vitamins	Amended, thank you (page 12)
Page 15 simple dextrose and electrolyte	Amended to glucose
It doesn't state anywhere the max glucose concentration for peripheral administration	That's because we don't know!
	"syringes and" added to lipid giving sets (page 16)
	"maternal" added – page 18
Query about total lipid requirement for term babies (table 2)	Consistent with ESPGHAN recommendation
Table 2 – Mg requirement 0 – 0 (??)	Corrected to 0 – 7.5
Nothing is discussed about urinary electrolytes. Does nowhere else measure them?	This has been added to page 6

Ingrid Grønlie and Hallvard Reigstad **NICU at Haukeland University Hospital, Norway**	
Comment	**Response**
	Note that this Framework for Practice refers to UK!
Birth weight criterion should be set higher, 1250 grams?	Amended as suggested
With optimal aa and glucose supplements most babies need K+ earlier	Amendments to page 6
Adding of supplements in pharmacy should be discussed. Bespoken PN in separate syringes are prepared several places in Norway, and information about additives to glucose and AA acid solutions as well as to TPN bags from the industry is readily available at the ward. Nurses prepare several infusions on the daily basis, like pressors, and the risk of contaminated PN solution is not higher than for these solutions (except for "pure" lipid solutions)	We acknowledge that preparation of PN fluids is still practised at ward level, but believe that this should be strongly discouraged
Why should triglycerides be measured when	Already addressed and text amended

acceptable concentrations are not defined	

Peter Mulholland, Pharmacist **Neonatal Intensive Care Unit** **Royal Hospital for Children, Glasgow**	
Comment	**Response**
In the draft WoS guideline we have <1250g as the cut off for absolute indication. (Tayside suggest 1500 g)	Absolute criteria for PN amended as suggested
Clarification on the glucose calorie content; I have seen a source that quotes 3.75Kcal/g. Licensed infusions in the UK all state 4Kcal/g which means that the MHRA don't know	Already addressed – see above
Zero sodium and potassium on Day 1. The current Scottish sodium free bag has potassium, but usage of the bag is small Also noted from Tayside: It recommends no sodium or potassium for the first 48 hours but our Scottish contract bags all contain potassium and we would potentially start sodium on day 2.	Already addressed – page 6
(From Leeds) According to ESPGHAN guidelines the maximum lipid concentration can be up to 4g/kg/day for pre-term neonates.	Thank you for pointing this out The text has been amended. We note that in practice, provision of 4 g/kg/day may be problematic since adding *Vitlipid* (10% lipid solution) to syringes reduces the fat concentration below 20%.
The definition of neonatal hyperglycaemia is confusing as on the text it states 2 values for hyperglycemia one at 6.9mmol/L and the other at >8.3mmol/L which is the cut-off value that was used on the study cited on the text.	"whole" added to blood glucose concentration. Hopefully more clear now
On table 2 the maximum glucose after 72h is 17g/kg/day, although on the text recommends up to 18g/kg/day as per ESPGHAN guidelines	Thank you - table 2 has been amended
(From Cardiff) We broadly agree with many of the points, including who should receive PN and the recommendations for energy, protein, electrolytes and lipids. We do however feel that using GIR (mg/kg/min) is more helpful than g/kg/day to prescribe glucose in neonates.	Both values have been given

<table>
<tr>
<td>We do not agree that daily or 12 hourly weighing is essential, our practice is to routinely weigh twice weekly and our medical team is satisfied that this is sufficient. We can (and do) weigh more frequently if necessary.</td>
<td>This is a matter for personal practice – the Working group agrees that routine weighing is very helpful (and greatly facilitated by incubator scales)</td>
</tr>
<tr>
<td>We do not agree with the view that insulin is as good as glucose reduction in the presence of hyperglycaemia. We don't feel there is sufficient evidence that supports this and the risk of refractory hypoglycaemia if the glucose line is tissued is too much for us.</td>
<td>As noted in the text, there is no evidence either way</td>
</tr>
<tr>
<td>While we do have access to a dietician, they are not directly involved with PN prescribing and we would disagree that safe PN prescription is not possible without a dietician being present.</td>
<td>We have stated that ideally dietetic input is available, but recognise that this may only be practical at network level – this should be seen as a tool to help achieve dietetic support in a level 3 NNU

Page 13 – "Ideally prescription of PN will involve a specialist neonatal pharmacist and a specialist neonatal dietitian as well as the clinician, but it is recognised that this may not be achievable in all NNUs."</td>
</tr>
<tr>
<td>(From Birmingham)

Birmingham

1.Main comments relate to provision of lipid provision in pre-term

In line with the text something like this might be clearer.

<table>
<tr><td>Lipid</td><td>First 24 hrs</td><td>24-48</td><td>48-72</td><td>>72-168hrs</td></tr>
<tr><td>g/kg/day</td><td>2</td><td>2.5</td><td>3.0</td><td>3.5</td></tr>
</table>
</td>
<td>As noted elsewhere, we have tried not to be too prescriptive in the document which is intended to be used alongside locally agreed guidelines. There is no published evidence in support of 0.5 g increments.</td>
</tr>
<tr>
<td>2.Clarity on fluid requirements of pre-term and term.

I do not seem to find clear guidance :-

<table>
<tr><td>Fluid</td><td>First 24 hrs</td><td>24-48</td><td>48-72</td><td>>72-168hrs</td></tr>
<tr><td>mls/kg/day</td><td>?</td><td>?</td><td>?</td><td>?</td></tr>
</table>
</td>
<td>The framework for Practice is deliberately vague about this – evidence is sparse, and we did not want to deter from the importance of clinical assessment of the baby in relation to fluid requirements</td>
</tr>
</table>

(From Barts) Some queries from our neonatal consultants about max calcium concentration for peripheral PN and was wondering if this could be included in the framework (seems difficult to calculate osmolarity).	Data not available!
Also, would be useful to have a section on managing liver complications associated with PN.	Out with the scope of this document

Sabita Uthaya Consultant Neonatologist & Honorary Senior Lecturer in Neonatal Medicine Chelsea and Westminster	
Comment	**Response**
My only comment would be that it is too broad and gives everyone carte blanche to carry on as they are. Given there have now been two trials of PN in this country one strong recommendation ought to be that clinicians use PN regimens that have been tested in the context of a RCT. With the safety data to back it. Or else we will carry on with folk doing what they have always done. BAPM has an opportunity to make a real impact in this area.	We accept all of these comments, but this is a document intended for broad use, and to set minimum standards. There is currently insufficient evidence to inform truly best practice and we have deliberately not been too prescriptive. Nevertheless, your comments are very relevant and so the executive summary has been amended to include " We note a need for clinicians, dietitians and pharmacists to keep abreast of new scientific evidence, *and whenever possible to use PN regimens that have been tested in the context of a randomised clinical trial with relevant safety data considered*. Further research including longer term metabolic and neuro-developmental outcomes is required to help to define optimal content and delivery of neonatal PN". Later in the text (under compounding of PN), we note that "Several standardised formulations of neonatal PN are currently available in the UK, including some concentrated formulae; *the composition of locally agreed PN solutions should be regularly reviewed and reflect the results of properly conducted randomised clinical trials with relevant safety data.*
There needs to be something said somewhere that the approach to PN initiation is different depending	Amendment to page 4 acknowledging that postnatal and gestational age will affect the balance of risk

on where in the course of postnatal life the baby is in.	versus benefit
Does this framework cover term babies?	Yes – amendment to page 4
I think a statement should be inserted here to say that it is acceptable to give PN peripherally	Amendment to page 5 “although PN may be administered peripherally (see below).
There should be a statement that extremely preterm babies are capable of tolerating up to 100 ml/kg/day of fluid on day 1	Page 5 – recommended starting volume changed to 60 – 100 ml/kg/day
Low intakes of sodium early on are required if one is to give phosphate.	Amendment already made Practice point 2 changed to • Only small amounts of sodium are generally required in the first 48 hours of life. • The table now acknowledges that phosphate cannot be given without sodium.
Using 8 g/kg/day in NEON PN with an incremental regimen of amino acids, preterm babies achieved the body composition equivalent to the term infant. Despite the low amounts of glucose there was still a significant percentage of babies that became hyperglycaemic. See the safety data table in the NEON report.	Consistent with Framework which recommends at least 5.6 g/kg/day.
Page 8 (maximum glucose 15 – 18 g/kg/day) This is a lot! I really do not think there is evidence to support these high intakes. Most of these babies would be increasing milk feeds during the period after birth. Saying 'should' in this sentence is too prescriptive in the absence of evidence. See my point about hyperglycaemia.	Point 2 softened to • For both preterm and term infants, glucose intake should be increased as tolerated. The maximum intake should not exceed 17.3 g/kg/day. This is consistent with ESGHAN recommendations. • The table has also been amended to indicate that glucaose intake after 72 hours should not exceed 17.3g/kg opposed to suggested a target range of 11-18 g/kg/day) •
Page 10 In NEON in the incremental arm at the maximum intake we had a ratio of 21.6 kcal /g of protein and in the RDI arm it was 18.2 kcal/g protein. But both groups had similar body composition and lean mass.	Point d amended to Although there is a paucity of evidence, it is likely that 20 - 25 non-nitrogen kcal are required per g protein) (10,15).
Smaller head size in high aa group in NEON is a	There are conflicting data regarding protein intake and early head growth (4,15) added as well as

concern.	significant rewording of protein section (page 10), particularly considering b).
Page 12 This point is not clear to me. Does this refer to lipid syringes mixed with vitamins? They are not more expensive	Previously amended
(Next paragraph) This sentence does not read well. The expert opinion is about the addition not the preparation.	"Based on expert opinion" has been deleted
Page 18 - I don't think one should be weaning PN as soon as enteral feeds are commenced.	Already amended to tolerating some enteral feed.