Pediatric Parenteral Nutrition

A Comprehensive Review
# Program Faculty

<table>
<thead>
<tr>
<th>Chair:</th>
<th>Maria R Mascarenhas, MBBS</th>
</tr>
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<tbody>
<tr>
<td>Section Chief, Nutrition</td>
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<tr>
<td>Division of Gastroenterology, Hepatology &amp; Nutrition</td>
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<td>Associate Professor of Pediatrics</td>
<td></td>
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<tr>
<td>University of Pennsylvania School of Medicine</td>
<td></td>
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<tr>
<td>Philadelphia, PA, USA</td>
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<table>
<thead>
<tr>
<th>Faculty:</th>
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<tbody>
<tr>
<td>Margaret Begany, RD, CSP, CNSC, LDN</td>
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</tr>
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<td>Children’s Hospital of Philadelphia</td>
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<tr>
<td>Philadelphia, PA, USA</td>
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</tbody>
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- Faculty has nothing to disclose

Speaker Disclosure goes here
Objectives

• To understand the history, indications, route of administration, components, monitoring, and complications related to parenteral nutrition for pediatric patients

• To understand the indications, components, and monitoring related to parenteral nutrition for neonatal patients

• To understand the role and implementation of parenteral nutrition in the critically ill and specialized patient populations

• To understand the background, implementation, monitoring, and complications related to home parenteral nutrition
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tbody>
<tr>
<td>AA</td>
<td>Amino acid</td>
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<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<tr>
<td>ASPEN</td>
<td>American Society for Parenteral &amp; Enteral Nutrition</td>
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<tr>
<td>Cr</td>
<td>Chromium</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>DRI</td>
<td>Dietary Reference Intakes</td>
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<tr>
<td>EN</td>
<td>Enteral nutrition</td>
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<tr>
<td>EFA</td>
<td>Essential fatty acid</td>
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<tr>
<td>EFAD</td>
<td>Essential fatty acid deficiency</td>
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<tr>
<td>G1R</td>
<td>Glucose infusion rate</td>
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<tr>
<td>HCI</td>
<td>Hydrochloric acid</td>
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<tr>
<td>HPN</td>
<td>Home Parenteral Nutrition</td>
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<tr>
<td>IBD</td>
<td>Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>iCa</td>
<td>Ionized calcium</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IVF</td>
<td>Intravenous fluid</td>
</tr>
<tr>
<td>IVF</td>
<td>Intravenous fat emulsion</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>MCT</td>
<td>Medium chain triglycerides</td>
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<tr>
<td>Mg</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Mn</td>
<td>Manganese</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>NEC</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Phos</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>PICC</td>
<td>Peripherally inserted central catheter</td>
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<tr>
<td>PN</td>
<td>Parenteral nutrition</td>
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<tr>
<td>PNALD</td>
<td>Parenteral nutrition-associated liver disease</td>
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<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
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<tr>
<td>REE</td>
<td>Resting Energy Expenditure</td>
</tr>
<tr>
<td>SBS</td>
<td>Short Bowel Syndrome</td>
</tr>
<tr>
<td>Se</td>
<td>Selenium</td>
</tr>
<tr>
<td>VLBW</td>
<td>Very low birth weight</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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- Parenteral Nutrition for the Pediatric Patient
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- Parenteral Nutrition for the Specialized Patient
- Home Parenteral Nutrition
- Cases
- Questions & Answers
Parenteral Nutrition For The Pediatric Patient
In 1966 an animal model of short bowel syndrome was created at the University of Pennsylvania. Beagle puppies were given PN via a central line and shown to have normal rates of growth. In the slide the puppies on the left received PN and had normal rates of growth as compared to the puppies on the right who did not have a central line.
The benefits of EN include: reduction of gut atrophy, improvement of gut motility, reduction in infections (enhanced gut immune function and avoidance of translocation), cost effectiveness and the fact that it is less likely to overfeed the patient.

The limitations of PN include that it is more likely to underfeed the patient. Contraindications to enteral feeding include: a nonfunctional gut, anatomical disruption, obstruction, ischemia, peritonitis and severe shock states; frequent interruptions for fasting for diagnostic and other procedures limit efficacy of EN, especially in malnourished patients and the risk of aspiration.

Parenteral Nutrition - Timing

- **Timing of nutrition may be as or more important than route**
  - A meta-analysis in adults compared early PN to the delayed start of enteral nutrition. They showed when early PN was used there was reduced mortality when compared to the delayed starting of EN. Patients who received PN had increased infections.

- **Pediatric Guidelines**
  - If EN is not possible, PN should be started within
    - 1-3 days in infants
    - 4-5 days in older children
  - Meta-analysis identified one trial in pediatric burn patients and concluded no difference when EN was started within 24 hrs compared to ≥ 48 hrs; therefore data insufficient!


Parenteral Nutrition – Indications

- Very low birth weight infants (birth weight < 1500 g)
- Inability to tolerate enteral feeds e.g. paralytic ileus, chemotherapy, radiation enteritis
- Small bowel obstruction
- Radiation enteritis
- Gastrointestinal fistula
- Hemodynamic instability with high risk of mesenteric ischemia (e.g., NEC in preterm infants, ECMO, shock, acute critical illness)
- Conditions associated with intestinal failure e.g., short bowel syndrome, diarrhea with irreversible malabsorption, pseudo-obstruction, intestinal epithelial disorders (microvillus inclusion disease, tufting enteropathy)
The best location for the tip of a central catheter is at the junction of the SVC and IVC with the right atrium. The danger of placing lines far into the right atrium relates to the possibility of perforation of the heart especially in very small neonates. Patients with renal failure are very fluid restricted thereby limiting the amount of PN calories that can be delivered. Altering the composition of the dialysis solution is a way to provide additional calories and nutrition.

The best location for the tip of a central catheter is at the junction of the SVC and IVC with the right atrium. The danger of placing lines far into the right atrium relates to the possibility of perforation of the heart especially in very small neonates. Patients with renal failure are very fluid restricted thereby limiting the amount of PN calories that can be delivered. Altering the composition of the dialysis solution is a way to provide additional calories and nutrition.

PN solutions containing 900 mosmol, according to ASPEN recommendation, or more should be given centrally. In adult patients 1800 mosmol is the maximum osmolality that should be used.

Some institutions may choose D10 or D12.5 based on osmolality or internal guidelines.

Non-tunneled catheters are easy to place, used only for the short term, should not be exchanged over a guidewire, are at high risk for infections and cannot be repaired. Tunneled catheters are meant for long-term usage, when plan for duration is greater than one month, require minimal care, requires the operating room or interventional radiology suite for placement and removal, have less infection risk and can be repaired. Picture shows an example of securing device for young children with central lines.


Traditionally PN solutions are 2-in-1 solutions with the IV lipid administered separately. This is still the solution of choice in many institutions since it allows for the easy identification of precipitates and for increased electrolyte administration. The 3-in-1 solutions are usually administered at home for ease of care, are being used in some pediatric institutions, and result in reduced nursing time.

Filters are placed in line between the PN solution and the patient and are very important.
Examples of other additives to PN include vitamin K, cysteine, carnitine, and insulin.
These are suggested macronutrient guidelines from AAP and ASPEN however there are other ways to calculate energy needs using accepted equations.

Usually the IV fat emulsion is 20% however 10 and 30% solutions are available; 30% are usually used in 3-in-1 solutions and 10% solutions are infrequently used.

20%

Carbohydrate content of PN is provided by dextrose. Carbohydrates provide calories and are important for glucose homeostasis. Stepwise increase by 0.5 - 1 mg/kg/min/day in extremely low birth weight infants (<1000 g) because of high risk for glucose intolerance.
These are the minimum intakes to meet the energy needs of the brain and other glucose dependent organs. If patients develop persistent hyperglycemia (>180 mg/dL) at these levels, calculate the GIR and consider insulin therapy instead of further reduction of dextrose concentration.

Web based calculators allow calculation of total GIR from multiple infusions with various dextrose concentrations (e.g. dextrose containing rider fluid + PN + dextrose medication carriers).

**Neonates need 5 - 6 mg/kg/min while adults glucose needs can be met with 1 - 2 mg/kg/min.**


Metabolic study in adults: as the glucose infusion rate is increased, the rate of oxidation begins to plateau. Above this point, glucose is being increasingly converted to fat.

Glucose Oxidation is Limited - II

Adapted from Wolfe et al. Metabolism 1980;29:892-900.
Components of PN - Protein

- Functions of protein
  - Provides structure (e.g., muscle)
  - Provides function (e.g., enzymes, transport proteins)
  - Acts as a nitrogen donor to other compounds (e.g., nucleic acids, carnitine, taurine)
- Protein should not serve as an energy source
- Protein requirements vary by age and disease state
- Infants
  - Infants need conditional amino acids like histidine, taurine and cysteine because of immature synthetic abilities
  - Infant amino acid solutions are based on the serum amino acid pattern seen in breastfed infants
- Excess protein intake leads to hyperazotemia

These are examples of commonly available amino acid solutions. Solutions vary depending on whether they are for infant or older children and they contain all the amino acids including essential, nonessential and conditionally essential. Taurine and cysteine are present in infant solutions.

Amino Acid Requirements in PN

- Amino acids

<table>
<thead>
<tr>
<th></th>
<th>g/kg/day</th>
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<tbody>
<tr>
<td>Preterm</td>
<td>2.5-4.0</td>
</tr>
<tr>
<td>Term infant</td>
<td>2.2-3.5</td>
</tr>
<tr>
<td>Child: 5-20 kg</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td>20-40 kg</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Adolescent</td>
<td>0.8-2.0+</td>
</tr>
</tbody>
</table>

*150 g/day maximum

- Increased protein needs
  - Malnutrition
  - Enteric/urinary protein loss
  - Stress
  - Drugs (e.g. corticosteroids)
  - Burns

Fat provides calories and meeting EFA needs.

In neonates triglyceride levels up to 200 mg/dL and in older children levels up to 300-400 mg/dL are tolerated.

Fat decreases the osmolality of the PN solution and is a more concentrated form of calories when compared to dextrose and amino acids.

Triene:tetraene ratio: If concentrations of the EFA are low, the ω-9 fatty acids are preferentially desaturated and elongated (i.e., 20:3 ω-9) so that the ratio of 20:3 fatty acids to 20:4 ω-6 (arachidonic acid derived from linoleic acid) is increased. Linoleic acid levels are also used to determine EFAD.

Test dose should be used in patients with egg allergy before administration of lipid solutions.

30% emulsions are available, but are used in 3-in-1 solutions only.

Use of IVFE is not contraindicated in patients with pancreatitis.

Shulman RJ, Phillips S. Parenteral nutrition in infants and children. J Pediatr...
This is the composition of a typical soybean emulsion compared to a fish oil and a SMOF emulsion. Fish oil emulsion is available from the FDA on a compassionate use basis. SMOF is used in Europe but not the USA. Note that DHA levels are highest in the fish oil emulsion.

Fish oil is not routinely available in North America; need IND from FDA. It contains predominately ω-3 fatty acids and approximately 4.4% and 1.8% linoleic and α-linolenic acids by weight of total fatty acids, respectively. Some evidence suggests it may reduce the severity of parenteral nutrition-associated cholestasis. It is unclear whether this is related to composition of the emulsion or reduced dosage of administration. It contains increased eicosapentaenoic and docosahexaenoic acid. In piglets there is a reduced risk for cholestasis which is not explained by difference in membrane fluidity, Na/K ATPase.

<table>
<thead>
<tr>
<th>Fatty Acids</th>
<th>Soy</th>
<th>Fish Oil</th>
<th>SMOF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic</td>
<td>50</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Linolenic</td>
<td>9</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Oleic</td>
<td>24</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Eicosapentaenoic</td>
<td>0</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Docosahexaenoic</td>
<td>0</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Arachidonic</td>
<td>0.1</td>
<td>2</td>
<td>1</td>
</tr>
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*Approximate % total fatty acids

* Soybean oil, medium chain triglycerides, olive oil and fish oil

http://www.tresenius-kabi.com/
Suggested Doses for Lipids

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose (g/kg/day)</th>
<th>Maximum Dose (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate/Infant</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Children</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adolescent/Adult</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Monitor levels closely and adjust daily in PN if needed. The goal is maintenance of homeostasis; weight based supplementation and altered by disease states.

- **Na**: Consider acid base balance, and fluids & diuretic therapy prior to adjusting Na in PN
- **K**: Consider renal function, diuretic therapy, GI losses, after load reducing agents, Na in PN, insulin, dextrose administration
- **Ca**: Consider phosphate level, bone health; elevated Ionized Ca (iCa) levels may be acceptable for certain patients
- **Phos**: Consider iCa levels, renal function, bone health
- **Calcium and phosphorus requirements are high in preterm infants**

**Components of PN - Micronutrient Guidelines**

<table>
<thead>
<tr>
<th>Daily Electrolyte Requirements</th>
<th>A.A.P.</th>
<th>A.S.P.E.N.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>2-4 mEq/kg</td>
<td>60-150 mEq</td>
</tr>
<tr>
<td>Potassium</td>
<td>2-4 mEq/kg</td>
<td>70-180 mEq</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.45-4 mEq/kg (infants &amp; toddlers)</td>
<td>10-40 mEq</td>
</tr>
<tr>
<td></td>
<td>0.45-3.15 mEq/kg (children)</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.5-2 mmol/kg</td>
<td>9-30 mmol/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.25-1 mEq/kg</td>
<td>8-32 mEq</td>
</tr>
<tr>
<td>Chloride</td>
<td>2-4 mEq/kg</td>
<td>60-150 mEq</td>
</tr>
</tbody>
</table>

Curves exist for Ca and Phos solubility and these are based on the type of the AA and pH of the solution. Factors affecting Ca and Phos solubility include temperature, concentration of Ca and Phos, type of AA product and concentration, dextrose concentration, pH of the final solution, cysteine, lighting, and order of the mixing.

Vitamin A is provided as retinol and vitamin E as tocopherol. Note; there is no vitamin K in MVI 12® and so it will need to be added at a dose of 0.2 mg. Other vitamins that can be added to PN: Insulin, Levocarnitine, folic acid, hydrochloric acid (only for ECMO patients), cysteine, and Vitamin K.

+++ http://www.hospira.com/Files/MVI_pediciatric_PI.pdf
++++ http://www.hospira.com/Files/MVI-12_PI.pdf
The current vitamin preparation for infants and children <11 years of age has not been reformulated since the early 1980s. Preparations used in children older than 11 years of age have been reformulated but should not be used for long periods of time in children <11 years of age to avoid excessive vitamin intakes. The evidence used to support recommendations is not comprehensive and more data is needed. Note that micronutrients may be lost due to adherence to the tubing and due to photodegradation. Note the differences in the recommendations from the manufacturer and the NAG-AMA group.

There are more than 60 minerals which are integrated into various body processes: chromium, copper, iodine, manganese, molybdenum, selenium, zinc etc. Zinc is often required in larger amounts than suggested. Iron may not be routinely included to PN solutions. Optimal requirements for trace elements for children are unknown. Higher amounts of trace elements are present in PN solutions due to component contamination.

Commercial products contain zinc, copper, chromium, manganese. In patients with liver disease copper and manganese doses often need to be adjusted. These 2 trace elements are excreted via bile and levels need to be monitored especially in patients with cholestasis. In patients with renal disease, selenium and chromium need to be used with caution and once again levels need to be monitored.

Manganese can be present as a contaminant in PN solutions. In patients on chronic PN may need to be eliminated due to high Mn levels. In patients on chronic PN, Cr supplementation may not be needed.

Other parenteral Fe preparations include Fe sucrose and Fe tri-phosphates. Fe Dextran is compatible with non-lipid containing PN. Due to the recent black box warnings, may want to consider administration of Fe Dextran under supervision, at least initially. When Fe Dextran infusions are used to treat Fe deficient anemia, a test dose is always administered and the patients closely monitored for allergic reaction.

Other causes of anemia in patients on PN are anemia of chronic disease, Zn and Cu deficiency, vitamin E and B12 deficiency, folic acid deficiency, and hemolysis and occult blood loss. In general oral route is preferred over parenteral route for treatment of Fe deficiency anemia.

In a retrospective adult study of 55 patients treated with home PN for more than 6 months, 30/55 (55%) had evidence of Fe deficiency anemia (10/30 at time of start of PN and 20/30 between 2-97 months after start of PN (mean age 28 months). Loss from GI tract was most prominent reason.

Zn is essential in the structural integrity of proteins, which regulate gene expression, and to nuclear binding proteins that act as transcription factors. It is a component of more than 250 metalloenzymes including alcohol, lactate and pyruvate dehydrogenases, alkaline phosphatase, and DNA and RNA polymerases. Zn losses may be high in proximal enterocutaneous fistulas.

Chronic Cu toxicity is illustrated in Wilson’s disease where high levels of Cu occur in the liver, brain, kidney, and other organs. The disease is manifested as cirrhosis of the liver, a variety of neurologic disorders, and renal damage. Premature infants are at special risk of becoming Cu deficient because Cu accumulates in the fetus during the third trimester. Marginal Cu deficiency can result in cardiac diseases, arthritis, loss of hair pigmentation, and neurologic abnormalities, mimicking vitamin B12 deficiency. Cu deficiency should be investigated among patients with pancytopenia in the face of cholestasis.


No Recommended Daily Allowance for Mn and published guidelines range from 1µg/kg/d to maximum of 40-100 µg/kg/day for patients > 40 kg. There is an increased risk for Mn toxicity in setting of hepatobiliary impairment and removal of Mn decreases accumulation of Mn in basal ganglia. Excessive doses of Mn are associated with cholestasis and can lead to CNS symptoms – insomnia, headache, increased forgetfulness, anxiety, rapid hand movements, and loss of coordination (Parkinson’s-like illness). Regular monitoring of patients receiving fixed doses of Mn over prolonged periods is recommended. Erythrocyte or whole-blood Mn concentrations appear to be
the most accurate and reproducible results.


It has been suggested that one should supplement if the patient is on exclusive pediatric PN for >4 weeks.

Experimental Se deficiency causes hypothyroidism.

Vinton NE, Dahlstrom KA, Stroble CT, Ament ME. Macrocytosis and
Changes in purification methods for PN solutions could lead to insufficient concentrations of Cr. If Cr were simply a contaminant, the amount of contamination in the body would increase with time. People still question whether or not Cr should be added to PN.
Chronic PN patients are at risk for Cr toxicity and evidence suggests that Cr should not be supplemented in these patients.

Components of PN - Miscellaneous

- Heparin 0.5 - 1 Unit/mL
  - May be added to prevent thrombophlebitis
  - Stimulates lipoprotein lipase and improves triglyceride clearance
- Insulin
  - May be used in patients with hyperglycemia
- Ranitidine
  - Compatible with PN when required
- Iodine
  - Not typically added to PN solutions
  - Currently may need to be added because of decreased use of iodine containing topical antiseptics.
- Be aware of compatibility issues with additives
  - Consult with your pharmacist

In the past there was adequate skin absorption of iodine from topical antiseptics BUT this may no longer be true with decreased use of topical antiseptics. Other possible additives include carnitine, cysteine, and insulin. For drug interaction and compatibility of medications, refer to the ASPEN core curriculum.

The concentration of the dextrose solutions used at the initiation of PN depends on the patient's serum glucose level, glucose content of currently administered fluids, type of catheter through which the PN solution will be administered and desired GIR. In general, can add goal protein except in the case of renal insufficiency or failure. Dextrose concentration can be advanced by 1 – 5% per day depending on the age of the infant, GIR, serum glucose levels and clinical status. IV lipid can be advanced by 0.5 – 1.0 g/kg per day depending on triglyceride levels.

The ideal non-protein calorie to nitrogen ratio or NPC:N ratio reflects the balance in the PN regimen between the non protein calorie (fat and carbohydrate) and protein calories. In stable patients, this ratio should be 150-250:1. This ratio may be less in critically ill patients or higher in renal failure patients. If an elevated BUN cannot be explained by changes in renal function, medications, bleeding or dehydration, then the ratio should be examined.

Fluid requirements can also be calculated using body surface area.


<table>
<thead>
<tr>
<th>Component</th>
<th>AAP</th>
<th>ASPIEN</th>
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<tbody>
<tr>
<td><strong>Protein</strong></td>
<td></td>
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<tr>
<td>10-20 kg</td>
<td>1.25 g/kg</td>
<td>&gt;10 kg or 1-10 yrs: 1.2 g/kg</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>0.8-2 g/kg</td>
<td>11-17 yrs: 0.8-1.5 g/kg</td>
</tr>
<tr>
<td><strong>Energy / Caloric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-20 kg</td>
<td>60-90 kcal/kg</td>
<td>&gt;1-7 yrs: 75-90 kcal/kg</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>30-75 kcal/kg</td>
<td>&gt;7-12 yrs: 50-75 kcal/kg</td>
</tr>
<tr>
<td>&gt;12-18 yrs</td>
<td></td>
<td>&gt;12-18 yrs: 30-50 kcal/kg</td>
</tr>
<tr>
<td><strong>Fluid</strong></td>
<td>&gt;10-20 kg = 1000 mL + 50 mL/kg &gt;10 kg</td>
<td>Carbohydrates should comprise 40% to 60% of total caloric intake.</td>
</tr>
<tr>
<td></td>
<td>&gt;20 kg = 1500 mL + 20 mL/kg &gt;20 kg</td>
<td>The minimum fat requirement is determined by essential fatty acid need, and the daily maximum is 50% to 60% of energy.</td>
</tr>
<tr>
<td><strong>Carbohydrates (Dextrose)</strong></td>
<td>10-20 kg: 8-28 g/kg</td>
<td>IV Fat Emulsion</td>
</tr>
</tbody>
</table>
Can use the suggested guidelines from AAP or ASPEN.


There are maximum amounts of electrolytes that can be added to the PN solutions based on solubility and risk of precipitation.

Patients do not need a dextrose rider during hours when they are not receiving PN. The is no true minimum weight to start cycling, but patients should be able to maintain normal glucose values while off PN solution and this is usually around a weight of 5 kg. A potential disadvantage of cycling PN is an increased risk of line infection.

Trophic feeds are considered any volume of feed that is less than 20% of goal.
Consider measuring carnitine (ester/free ratio) levels in patients who are NPO for a significant amount of time, as indicated. Some clinicians feel that measuring carnitine levels is not helpful.

Consider checking iCa in patients with low albumin levels.
Consider measuring carnitine levels in patients who are NPO for a significant amount of time, as indicated. Some clinicians feel that measuring carnitine levels is not helpful.
Thyroid function can be checked (TSH) at baseline, if indicated, and yearly.
Consider checking prothrombin time weekly, and then monthly.
Consider measuring urine Na levels to assess adequacy of Na intake especially in patients with SBS and growth problems.
During PN initiation it is customary to follow serum electrolytes closely.

Overfeeding leads to increased fat synthesis with an increase in RQ (CO$_2$/O$_2$), leading to CO$_2$ retention. Excessive CHO intake leads to hypercarbia, hypertriglyceridemia, hyperinsulinemia.

Patients on chronic PN, especially HPN, are at risk for nephropathy. This may be related to subclinical renal damage from components of PN, cumulative drug toxicity from nephrotoxic antibiotics used to treat central line infections.


Central line associated blood stream infections (CLABSI) or Catheter related blood stream infection (CRBSI); both terms have been used to describe infections associated with central line venous catheters. The infection may be situated within the catheter, within the tunneled portion of the catheter and surrounding tissue, or at the exit site.

Need to differentiate between a central line infection and colonization. About 22% of all hubs are colonized with bacteria. Infections may be hard to recognize as some patients may be febrile only during PN infusions or when the central line is flushed. A white blood cell count may be normal in circumstances where the infection is at the exit site.


The recommendations are that the tubing for lipids be changed every 12-24 hours and the dextrose tubing be changed every 72 hours unless it is a 3-in-1 solution.

Parenteral Nutrition - Mechanical Complications

- Catheter-related
  - Pneumothorax
  - Hematoma
  - Hemothorax
  - Malposition
  - Venous and intracardiac thrombosis
  - Air embolism
  - Catheter blockage / migration
  - Transient arrhythmias, perforation of the heart
  - Superior vena cava syndrome

- Infusate-related
  - Extravasation into local tissues, pericardium, peritoneum, thorax, mediastinum, liver and scalp
Non-thrombotic occlusions are caused by calcium phosphate precipitates, medication precipitates, lipid residue, or mineral precipitates. Thrombotic catheter occlusions are usually treated with thrombolytics. The use of 0.1N hydrochloric acid is most effective for clearing catheter occlusions due to precipitation of calcium-phosphate. For catheter occlusions due to precipitates associated with medications in the high pH range such as tobramycin and phenytoin, sodium bicarbonate 1mEq/mL has been anecdotally reported to be effective. 70% ethanol is the most effective solvent to dissolve lipid residue. NaOH may be used to dissolve mineral precipitates.

Picture insert is of an occluded line.
This is a picture of a child with EFAD on the left, and on the right after he was successfully treated.

Parenteral Nutrition - Refeeding Syndrome

• Definition
  – Severe fluid and electrolyte shifts (especially Phos and K) in malnourished patients undergoing rapid nutritional rehabilitation either enterally or parenterally. Can be avoided by supplementation with Phos, Mg and K.

• Risk Factors
  – Chronic malnutrition, anorexia nervosa, morbid obesity with massive weight loss, patients not fed for 7-10 days with evidence of stress and depletion

• Clinical
  – Low serum Phos, Mg, and K levels, acute respiratory and circulatory collapse

• Treatment
  – Start with providing 50-75% estimated energy needs or give current intake.
  – Increase kcals by 10-20% daily until goal reached; monitor labs, vital signs, fluids.
  – Provide adequate protein.

Parenteral Nutrition – Aluminum

- Contaminant of PN ingredients
- Accumulates in bone
- Developmental delay in preterm infants
- High levels of aluminum present in Ca, Phos, heparin, albumin solutions, and some antibiotics
- 2004 FDA mandate to report amounts in commercial products
- Can be measured in blood

This is a slide of a bone and the blue staining represents aluminum deposition.

Sulfite are added to crystalline amino acid products to diminish amino acid oxidation. Acute and delayed sensitivity reactions can occur after ingestion of sulfite-containing foods and other products. Bisulfite reacts with disulfide bonds to alter protein structure/configuration thus potentially affecting antigenicity. Evidence for this includes the fact that bisulfite and sulfur dioxide can precipitate asthmatic attacks and that bisulfite additives can interact with other components (lipids) and cause sensitization.

Butylated hydroxyanisole (BHA) and Butylated hydroxytoluene (BHT) are added to Pediatric MVI® as preservatives. Oral BHA and BHT are associated with allergy symptoms. Polysorbate emulsifiers are added to E-Ferol parenteral solutions. Polyethyleneoxylated castor oil is added to Cremophor MVI® preparations.

Allergic reactions to soy are common but are more prevalent in Japan than in the USA, and relates to soy-based lipid emulsions. In general the allergy is usually attributed to soy protein and therefore a reaction to soy oil is less likely. Patients can have frequent reactions to other legumes (peanut, lentils, garbanzo beans, peas). There are 15 different proteins that can be potential antigens though P34 protein responsible for 75% of reactions. There is a higher risk to those with egg allergy.

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**Parenteral Nutrition - Adverse Reactions**

- Extremely rare
- Less than 20 cases of parenteral nutrition reactions reported in the literature among adults and children
  - Nearly half with history of malignancy
  - 15% with history of medication or food allergies
- Reported causes
  - Site prep: Chlorhexidine
  - Bottle stoppers; Latex
  - Lipid emulsion
  - Amino acid solution
  - Multivitamins
  - Fe Dextran

The etiology of metabolic bone disease seen in patients on chronic PN is unclear and probably multifactorial. It may be related to altered vitamin D metabolism, Cu and vitamin K deficiency, and aluminum toxicity. Clinically patients present with bone pain (back pain) and pathologic fractures. Aluminum toxicity is known to occur in the brain, bone and liver causing bone pain, metabolic bone disease, osteoporosis, patchy osteomalacia, reduced bone aposition and fracturing osteomalacia, encephalopathy and impaired neurological development. However Advenier et al showed in 10 children (avg age 8 year) on PN for an average of 6.5 years, elevated aluminum levels with no associated symptoms.

Bone specialist: physician with experience treating pediatric patients with bone disease, often endocrinologist. The workup for patients with metabolic bone disease include parathormone, vitamin D levels (25 hydroxy and 1,25hydroxy), alkaline phoshatase, alkaline phosphatase.
isoenzymes including bone specific alkaline phosphatase, serum Phos, Ca, Mg and Cu levels, and urine Ca, creatinine and Phos levelss.

Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; 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 of Paediatric Research (ESPR). J
Treatment considered decreasing IV fat emulsion, start EN if only trophic, wean PN or adjust PN components.

Ovchinsky N. Conjugated bile acid as potential early markers of parenteral nutrition associated liver disease. JPEN 2010;34(5):472-473
Ursodeoxycholic acid is often used but limited data on its effectiveness.


Parenteral Nutrition - Conclusions

- PN can be lifesaving in patients with limited tolerance of enteral nutrition
- Development of a PN regimen should take into account the age and clinical condition of the patient
- The practitioner must be aware of the risks of PN
- Monitoring is key to successful therapy
Neonatal Parenteral Nutrition

Neonatal PN

- Early initiation of nutrition is critical for the neonate.
- PN should be initiated in infants who are not likely to achieve total enteral nutrition within the first week of life.
- Trial of aggressive PN on the first day of life (versus later start)
  - Fewer infections
  - Neonates more likely to be > 10th percentile for weight at discharge
- Protein is required to decrease or prevent catabolism, especially in infants who are ill.
- Early delivery of amino acids improves glucose tolerance.
Neonatal PN - Indications

- Inability to start or advance feeds within first 1 - 2 days for preterm or VLBW infants; or within 3 - 5 days for term infants
- Necrotizing Enterocolitis (NEC)
- Functional immaturity of the gastrointestinal tract or gestational age at birth < 30 - 32 weeks
  - Use while advancing enteral feeds
- Unrepaired congenital gastrointestinal anomalies
  - Gastroschisis, bowel atresias, omphalocele, cystic fibrosis with meconium ileus, Hirschsprung’s disease, ileus
- Short Bowel Syndrome
- Increased risk of NEC due to impaired gastrointestinal perfusion
  - Patent ductus arteriosus, hypotension, indomethacin therapy, etc.

Example Starter PN
• Dextrose 7.5% OR 10 %
• Trophamine 4%
• Calcium gluconate 2000 mg/L (9 mEq/L)
• Heparin 0.5 units/mL
• Total volume: 250 mL
• Rate: 60 mL/kg/day
Neonatal PN - Goals

• Primary goals
  – To provide adequate energy and protein to prevent negative energy and nitrogen balance
  – To prevent essential fatty acid deficiency
  – To support normal growth and development
  – To decrease morbidity
Neonatal PN - Calculations

- Use birth weight for calculations until birth weight regained. Thereafter, daily weight is used in calculations.
- Use an estimated dry weight for calculations when indicated.
- Monitoring growth is essential
  - Daily weight
  - Weekly length and head circumference
Two options for calculation of PN volume for infants who are also receiving enteral feeds:

(a) determine the total volume of the day’s enteral feedings; then order the remainder of fluid and component needs as PN. This will require daily recalculation of parenteral composition, or

(b) order the PN solution as if the infant were NPO, but only administer the amount of PN needed to supply the volume NOT provided
by enteral feedings. The parenteral nutrition composition will vary minimally. The cost of the unused solution is negligible; be aware that the patient will only get a percentage of the micronutrients in the PN bag.

Smaller preterm infants are prone to hyperglycemia and may require a limited GIR or insulin to attain normal glucose levels. The maximum dextrose concentration depends on tolerance and access. A higher GIR is required to compensate for calories when lipids are restricted (e.g. cholestasis prevention, hypertriglyceridemia). Consider advancing GIR daily by 0.5 - 1 mg/kg/min per day for VLBW premies; 1 - 1.5 mg/kg/min per day for term infants.

These are examples of amino acids solutions used in infants. Solutions contain all the amino acids including essential, nonessential and conditionally essential. Taurine and cysteine are present. Please ensure that you check the specific product websites regarding updates.
Neonatal PN - Protein

- Protein requirements

<table>
<thead>
<tr>
<th></th>
<th>Preterm infants</th>
<th>Term infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-3.5 g/kg/d</td>
<td></td>
</tr>
<tr>
<td>Preterm infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6 months</td>
<td>2.5-3 g/kg per day</td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td>2-2.5 g/kg per day</td>
<td></td>
</tr>
</tbody>
</table>

- Generally start amino acids at 2-3 g/kg per day
- Traditional step-wise advance of protein
  - No benefit and may be associated with a negative nitrogen balance due to delay in reaching target protein intakes
- Higher protein intakes up to a maximum of 4 g/kg per day should be considered for infants with protein losses or healing needs. (e.g. extremely low birth weight infants, chest tube losses, wound dehiscence, etc.)

Neonatal PN - Lipid

• Provides essential fatty acids
• Concentrated source of calories (20% solution = 2 kcal/mL)
• 20% emulsion is preferable
  - Lower volume requirement
  - Improved triglyceride clearance over 10% emulsion
• May prolong integrity of peripheral intravenous line due to low osmolarity
• Lipid emulsions in the US are either based on soybean oil or a combination of safflower and soybean oil
This is a picture of a child with EFAD on the left, and on the right after he was successfully treated.

The hang time for lipids is 24 hours for central venous catheters and 12 hours for peripheral catheters.


CDC website: [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5110a3.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5110a3.htm)

## Neonatal PN - Lipid Infusion & Clearance

- Most commonly infused over 20 - 24 hrs
- Maximum infusion rate is 0.15 g/kg/hr
- Poor lipid clearance may be seen with immaturity, infection, stress, liver disease, corticosteroids, or malnutrition.
- No conclusive evidence for restriction of IVFE in infants with unconjugated hyperbilirubinemia
- Provided as a separate infusion from dextrose and amino acid solution to enhance Ca and Phos solubility (not as 3-in-1 solution)
Evidence emerging for restriction of IVFE to prevent or treat PN associated cholestasis. Alternate lipid forms not commercially available in the US (e.g. Omegaven) are utilized for prevention and treatment of PN associated cholestasis,

Neonatal PN - Heparin

- Prophylactic to prevent thrombosis
- Reduces formation of fibrin sheath around catheter
- May reduce phlebitis with peripheral intravenous access
- May facilitate lipid clearance—increased lipolysis and release of free fatty acids
- Reduces the incidence of culture-positive catheter-related sepsis
- Heparin dosing:
  - 1 unit/mL full-term infants-adults
  - 0.5 units/mL preterm and VLBW infants (<1500g)

Uslu et al. J Perinatol. 2010 [Epub]
Other published guidelines suggest a frequently used pharmacological intravenous dosage of 10 – 20 mg/kg/day with a maximum dosage of 100 mg/day. However, these dosages are much higher than typical dietary intake and several studies suggest better results with lower doses. Negative effects were exhibited with doses of 48 mg/kg/d in parenterally fed preterm neonates.

The adult dose is 2-5 mg/kg/day. Some institutions may use a dose 10 mg/kg/day for maintenance and a dose of 20 mg/kg/day if deficiency exists. Dose can adjusted based on levels.

Dose can be adjusted based on levels (ester/free ratio)

The patient may be getting electrolytes from other sources e.g. umbilical arterial catheter, arterial lines, medications, fluid and electrolyte boluses. Calculation of daily intake should take into consideration these factors and what the patient has received in the last 24 hours.
Consider measuring urine Na levels to assess adequacy of Na intake especially in patients with SBS and growth problems.
During PN initiation it is customary to follow serum electrolytes closely.
These are suggested daily electrolyte and mineral requirements. Usually start at the lower end of the dose range. Acetate should be used to correct acidosis and Na or K salt may be used based on serum electrolyte levels.

Some practitioners may feel that these differences in Al content are not significant and do not warrant selection of K acetate over Na acetate.

Factors affecting calcium and phosphorus solubility in PN include the following:

- Absolute amounts of calcium and phosphorus, form of calcium salt (calcium gluconate allows improved solubility), order of mixing, pH of the solution (acidic pH allows improved solubility), temperature, amino acid content and composition, dextrose concentration and presence of other additives. Check with your pharmacist or use computer software available to assist with determination of calcium and phosphorus solubility.


Neonatal PN
Calcium/Phosphorus Solubility & Cysteine

- Cysteine is considered to be an essential amino acid for preterm infants
- Can be added to PN solution
- Lowers pH of the solution allowing increased solubility of Ca and Phos
- Dosing recommendation is 40 mg cysteine per g of TrophAmine®
- Addition of cysteine may necessitate supplementation with acetate in preterm infants and possibly other patients prone to acidosis

Use of adult preparations for infants <1500 g may present a danger due to the infant’s inability to metabolize propylene glycol and polysorbate additives.

Vitamin C is especially prone to degradation by oxygen. Only 35% of vitamin C remained after 24 hrs when stored at 4°C; only 15% remained after 24 hrs when stored at 21°C. Light exposure from phototherapy results in exposure of the neonate to peroxidation products.


### Neonatal PN

#### Examples of Multivitamin Pediatric Products

<table>
<thead>
<tr>
<th>MVIT&lt;sup&gt;®&lt;/sup&gt; Pediatric</th>
<th>INFUVITE&lt;sup&gt;®&lt;/sup&gt; Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 mL</strong></td>
<td>2 vial system (4 mL of vial 1, 1 mL of vial 2)</td>
</tr>
<tr>
<td>Vitamin A: 2300 IU</td>
<td>Vitamin A: 2300 IU</td>
</tr>
<tr>
<td>Vitamin D: 400 IU</td>
<td>Vitamin D: 400 IU</td>
</tr>
<tr>
<td>Vitamin E: 7 IU</td>
<td>Vitamin E: 7 IU</td>
</tr>
<tr>
<td>Vitamin K: 200 mcg</td>
<td>Vitamin K: 200 mcg</td>
</tr>
<tr>
<td>Vitamin C: 80 mg</td>
<td>Vitamin C: 80 mg</td>
</tr>
<tr>
<td>Thiamin 1.2 mg</td>
<td>Thiamin 1.2 mg</td>
</tr>
<tr>
<td>Riboflavin 1.4 mg</td>
<td>Riboflavin 1.4 mg</td>
</tr>
<tr>
<td>Niacin 17 mg</td>
<td>Niacin 17 mg</td>
</tr>
<tr>
<td>Dextrohedrol 5 mg</td>
<td>Dextrohedrol 5 mg</td>
</tr>
<tr>
<td>Vitamin B6: 1 mg</td>
<td>Vitamin B6: 1 mg</td>
</tr>
<tr>
<td>Vitamin B12: 1 mcg</td>
<td>Vitamin B12: 1 mcg</td>
</tr>
<tr>
<td>Biotin 20 mcg</td>
<td>Biotin 20 mcg</td>
</tr>
<tr>
<td>Folic acid 140 mcg.</td>
<td>Folic acid 140 mcg</td>
</tr>
</tbody>
</table>

**Infants >3kg:** 100% of the standard dose (5 mL)
- Infants 1-3kg: 65% of the dose (3.25 mL)
- Infants <1kg: 30% of the dose (1.5 mL)

Infants ≥3 kg: 100% of Vial 1 (4 mL) & Vial 2 (1 mL)
- Infants 1-3 kg: 65% of Vial 1 (2.6 mL) & Vial 2 (0.65 mL)
- Infants <1 kg: 30% of Vial 1 (1.2 mL) & Vial 2 (0.3 mL)

[http://www.hospira.com/Files/MVI_pediatric_PI.pdf](http://www.hospira.com/Files/MVI_pediatric_PI.pdf)
Because of elevated levels of water-soluble vitamins, the current proposal is to reduce the intake of water-soluble vitamins and increase retinal.

In 1988 Greene et al reviewed the use of vitamins in infants and children on PN. They compared the current recommendations at that time to what they considered was their best estimate for new formulations.


There are more than 60 minerals which are integrated into various body processes: chromium, copper, iodine, manganese, molybdenum, selenium, zinc etc. Zinc is often required in larger amounts than suggested. Iron may not be routinely included to PN solutions. Optimal requirements for trace elements for children are unknown. Higher amounts of trace elements are present in PN solutions due to component contamination.

Commercial products contain zinc, copper, chromium, manganese. In patients with 


Zinc is essential to the structural integrity of proteins, which regulate gene expression, and to nuclear binding proteins that act as transcription factors. It is a component of more than 250 metalloenzymes including alcohol, lactate and pyruvate dehydrogenases, alkaline phosphatase, and DNA and RNA polymerases.

Neonatal PN – Copper (Cu)

- Decrease or omit with cholestasis (risk for toxicity due to biliary excretion of Cu)
  - Case reports of deficiency when decreased or omitted in PN
  - Premature infants are at special risk of becoming Cu deficient because Cu accumulates in the fetus during the third trimester
  - Consider checking Cu and ceruloplasmin levels (and using clinical circumstances) to guide dose adjustments, especially with cholestasis


Neonatal PN – Selenium (Se) & Chromium (Cr)

• Selenium:
  - Should be provided to all patients at initiation of PN
  - Omit in patients with renal disease
  - Increased requirement with oxidative stress, critical illness, losses (e.g. fistula output, burns, drains)
  - Se status: monitor plasma Se together with a measure of systemic inflammation (↑ C-reactive protein is associated with ↓ plasma Se)

• Chromium:
  - Recent data suggests need to lower the recommended amount of Cr in PN.
  - Omit in patients with renal disease

Other parenteral Fe preparations include Fe sucrose and Fe tri-phosphates. Fe Dextran is compatible with non-lipid containing PN. Due to the recent black box warnings, may want to consider administration of Fe Dextran under supervision, at least initially. When Fe Dextran infusions are used to treat Fe deficient anemia, a test dose is always administered and the patients closely monitored for allergic reaction.

Other causes of anemia in patients on PN are anemia of chronic disease, Zn and Cu deficiency, vitamin E and B12 deficiency, folic acid deficiency, and hemolysis and occult blood loss. In general oral route is preferred over parenteral route for treatment of Fe deficiency anemia.

In a retrospective adult study of 55 patients treated with home PN for more than 6 months, 30/55 (55%) had evidence of Fe deficiency anemia (10/30 at time of start of PN and 20/30 between 2-97 months after start of PN (mean age 28 months). Loss from GI tract was most prominent reason.

Consider checking iCa in patients with low albumin levels.
Consider measuring carnitine levels in patients who are NPO for a significant amount of time, as indicated. Some clinicians feel that measuring carnitine levels is not helpful.
Thyroid function can be checked (TSH) at baseline, if indicated, and yearly.
Consider checking prothrombin time weekly, and then monthly.
Neonatal PN - Monitoring Triglycerides

- Serum triglyceride levels are often used to monitor clearance of intravenous fat emulsion
  - Levels less than 200 mg/dL are acceptable
  - Consider checking the level prior to start of intravenous fat emulsion and after any increase in rate of the emulsion
  - With decline in overall clinical status
  - Monitor every 1 - 2 weeks once the patient is on a stable regimen


Neonatal PN - Discontinuing Parenteral Nutrition

- When adequate hydration is attained from enteral or oral feedings
- When the infant is
  - Tolerating enteral feedings
  - Receiving $\leq 25 \text{ mL/kg per day of PN}$
- The rate of dextrose administration should be tapered to prevent rebound hypoglycemia
Parenteral Nutrition For The Specialized Patient
Parenteral Nutrition – Specialized Patient

- Critical Illness
- Inflammatory Bowel Disease (IBD)
- Short Bowel Syndrome (SBS)
- Liver
- Renal
- Oncology
- Metabolic
Some experts believe that gut atrophy does not occur in humans. Bacterial translocation due to gut atrophy or PN has not been conclusively demonstrated in human and when it has been shown it was not clinically meaningful (personal communication, A. Buchman)

Critical Illness - Timing

- Timing of nutrition may be as or more important than route
  - A meta-analysis in adults compared early PN to the delayed start of enteral nutrition. They showed when early PN was used there was reduced mortality when compared to the delayed starting of EN. Patients who received PN had increased infections.

- Pediatric Guidelines
  - If enteral nutrition not possible, parenteral nutrition should start within
    - 1-3 days in infants
    - 4-5 days in older children
  - Meta-analysis identified one trial in pediatric burn patients and concluded no difference when enteral nutrition was started within 24 hr compared to ≥ 48hr. therefore data insufficient to make firm recommendations

Severe injury is associated with a constellation of signs and symptoms commonly known as the systemic inflammatory response syndrome (SIRS). This syndrome reflects the metabolic response to injury at a central (neuroendocrine) level and at a local tissue (at the site of injury) level that leads to end organ damage from the release of systemically active mediators. The injury can be burns, surgery or trauma. The mediators include cytokines, chemokines, nitric oxide and fatty acid derived eicosonoids. End organ damage can be severe and present as multi-organ failure.
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This data is from a review based largely on opinion and clinical experience.

The hypometabolic phase often lasts a day and is dominated by the neuroendocrine response to injury initiated through the ACTH - cortisol - catecholamine pathways as well as the acute vascular responses to injury that presents as acute shock. Tissue, including gut ischemia predominates in this phase. This hypometabolic phase is diminished due to brain death and hypometabolism dominates independent of tissue injury.

The subsequent hypermetabolic phase lasts days and is dominated by the production of cytokine, endotoxin and reactive oxygen metabolites which are produced in response to injury, inflammation and often sepsis. Tissue reperfusion occurs at this stage.

The mediators of the recovery phase often set up competing pro-inflammatory and anti-inflammatory (compensatory anti-inflammatory response syndrome or CARS) or immune suppressing pathways, leading to considerable complexity in this system and how the patient presents (early or late multi-organ failure).

Furthermore the entire process is made more complex by ‘secondary hits’ e.g. need for surgery and sepsis. The patient is at high risk given reduced gut function and
bacterial translocation and decreased immune function.

In **healthy** states our normal response to **fasting** is first to mobilize glycogen stores from the liver. Amino acids are used for gluconeogenesis as glycogen is depleted and as glucose is quickly depleted as a fuel, triglycerides are mobilized from adipose tissue. These mobilized **free fatty acids predominate as the fuel source in fasting.** Multiple hormones are involved including glucagon and growth hormone. Conversely our normal response to **feeding** is insulin release resulting in glucose uptake, oxidation and glycogen production. Triglycerides are stored in adipose tissue. **Glucose is the primary fuel source.**

In **critical illness** both glucose and fatty acids are mobilized as a fuel source. At the same time as an aberrant metabolic response dominated by stress hormone (cortisol and catecholamines), cytokine release and insulin and growth hormone resistance occurs. Muscle protein breakdown provides amino acids for gluconeogenesis and acute phase and immune proteins. Glycogen breakdown and increased glucose uptake leads to rapid release of lactate. Glucose feeding leads to hyperglycemia and lipolysis is not suppressed so that simultaneously there is an increased free fatty acid production and hence triglycerides from their hepatic conversion. This situation makes the individual vulnerable to overfeeding.

Aberrant intermediary metabolism leads to excess energy substrates and so providing more non-protein energy may only increase the potential risks of hyperglycemia and excess free fatty acids and hence triglycerides.

High glucose levels in children with critical illness are associated with more mortality, length of stay and ventilator days, particularly given concomitant sepsis. Poor diabetic control is also associated with poor wound healing and sepsis and supports the role of elevated circulating glucose in critical illness. Further support from in vitro work showing increased extracellular glucose contributes to impaired immune (particularly neutrophil function) and anti-oxidant defences (stimulates generation of reactive oxidant species). Excess glucose undergoes oxidation, increasing VCO2 and this can increase work of breathing and will increase lipogenesis: excess fat, stored in the liver as steatosis.

Lipoprotein lipase dysfunction in critical illness places patients at increased risk of lipid overload syndrome from parenteral lipid. Excess lipid delivery in the face of poor lipid clearance contributes also to hepatic steatosis and concerns over sepsis, given pro-inflammatory lipid pathways.

Some experts believe that while there is theoretical risk of increased PCO2 with overfeeding, there is limited data to indicate prolonged ventilator weaning. Fat overload syndrome occurs when patients get very high doses of intravenous lipid. This can occur when the dextrose amino acid solution and IV fat emulsion administration rates are interchanged and the patient gets a very high dose, or
sometimes a total daily dose, of IV fat emulsion over a short period of time. Clinically the patient will have an elevated triglyceride level tachypnea, hypoxia, thrombocytopenia. Therapy for the fat overload syndrome is supportive. The risk for pancreatitis occurs with elevated triglyceride levels of greater than 1000 mg/dL.

The critical care patient is also at risk of not meeting intended nutrient delivery due to the following reasons:
1) frequent interruptions from fasting for procedures or investigations
2) limitations in fluid delivery and need for fluid restriction
3) delayed introduction of caloric feeding and the difficulties in accurately predicting calorie requirements (predicting energy requirements).

Pediatric patients admitted to intensive care are known to frequently have baseline malnutrition. The combination of a catabolic state with critical illness and the risk of underfeeding along with a cumulative energy deficit promote worsening of that underlying malnutrition during the ICU stay.

Specifically as patients enter the recovery phase of the systemic inflammatory response and when they begin enteral feeding, they are at risk of not having calorie delivery increased to meet the requirements for tissue repair, re-emerging growth potential and increased thermic effect of food.

Malnutrition is common in children admitted to PICU (Hulst et al) and worsens over the length of stay.

The main prognostic factor is loss of lean mass – associated most importantly with increased mortality (Pollack et al).


These investigators have shown that one quarter of children admitted to ICU are likely to have malnutrition based on anthropometric measurements and these same measurements worsen during intensive care stay directly correlated with the length of stay.
We used to think that hypermetabolic patients required more energy however this is not the case! Factors to explain this are documented on this slide and these include:

1) neuro-protection through cooling,
2) lack of thermic effect of enteral feeding,
3) use of drugs like sedatives, beta blockers and morphine.

There is a notable individual variability in REE that is difficult to predict. In general however we can now state that burns is one of the few clinical situations with a significant increase in REE. Few drugs – again a notable exception being catecholamines - will increase REE in the ICU setting.

In addition while head trauma patients are often paralyzed and sedated, they have a specific hypermetabolic response (driven by central hormonal aberrations in the systemic inflammatory response) that may lead to increased REE and in this population measurement of EE, rather than use of prediction equations may be particularly important.


Verhoeven JJ, Hazelzet JA, van der Voort E, et al. Comparison of measured and predicted energy expenditure in mechanically ventilated children. *Intensive Care*
More information can be found on energy expenditure via the following references:


Protein turnover is increased in critical illness, but in general a negative nitrogen balance results as protein breakdown is increased over synthesis


Glutamine is not commercially available in the USA. Some experts consider its use investigational since it is not FDA approved.


Notable Pediatric trials:
### Critical Illness - Specific Amino Acids II

- **Arginine**
  - Non-essential amino acid, essential in neonates, conditionally essential in stress
    - Ammonia detoxification, nitric oxide synthesis
  - Endogenous arginine production is dependent on gut metabolism
    - Expect low plasma levels in fasting states
  - No pediatric data
    - Role as ‘immunonutrient’ limited by lack of data & confounding factors in studies

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It has been suggested that phytosterols content of IV lipid may be related to PNALD.


Specific Conditions - ECMO

- REE not readily predictable leading to risk of overfeeding
- PN historically was used because of concern of decreased splanchnic perfusion with feeding
- But enteral nutrition **not** contraindicated; can be safe alternative
  - See ASPEN Guidelines for nutrition support for neonates supported by ECMO
  - Risk for hyperbilirubinemia with ECMO


Other references of interest:

Chest tube losses can include high amounts of protein and electrolytes, especially Na, Zn, and fat. Need to monitor patient for EFAD if chest tube losses are prolonged.

Specific Conditions - Chylothorax

- Common indication for parenteral nutrition in critical care (especially post cardiac surgery)
- Parenteral lipid is not contraindicated
- Availability and efficacy of enriched MCT enteral formulas should limit need for parenteral nutrition support
- Replace chest tube losses
  - Protein
  - Electrolytes
  - Zn
Zn losses are high from ostomies and proximal enterocutaneous fistulas.

IBD - Considerations for Use of PN

- Intolerance to enteral feeds
- Restricted enteral intake/severe perianal disease
- Fistulas, perforation and intra-abdominal abscesses
- Toxic megacolon
- Intestinal obstruction
- Perioperative nutrition rehabilitation
- Short bowel syndrome
- Unable to sustain growth on enteral feeds
Dietary studies in patients with IBD namely Crohn’s disease have shown decreased intakes of Zn, Cu, Fe, Ca, folic acid, vitamin C and vitamin D when compared to controls and the RDA. Essential fatty acid status may also be altered. Fat soluble vitamin deficiencies and vitamin B12 can occur in patients with ileal disease and/or resection. Lower BMD that is commonly seen in patients with Crohn's disease may be related to vitamin D and K deficiency.


Azcue M, Rashid M, Griffiths A, Pencharz PB. Energy expenditure and body composition in children with Crohn's disease: effect of enteral nutrition and


SBS/Intestinal Failure
Nutritional Considerations I

- PN should be used to meet energy needs when EN is insufficient or cannot be tolerated
- Start trophic enteral feeds when possible and advance as tolerated
- Cycle PN regimen when possible
- Energy needs to be provided for treatment of malnutrition and to promote normal growth
  - Prediction equations may be helpful but the patient's response is the best guide to adjusting caloric intake
  - Avoid overfeeding and provide adequate calorie intake for normal linear growth

SBS/Intestinal Failure
Nutritional Considerations II

- Increased requirements in patients with gastrointestinal losses
  - Fluid
  - Zn
  - Bicarbonate – needs to be replaced as acetate in PN
  - Na (especially in ileostomies): patients will not grow until adequately supplemented; urine Na measurements can be used to guide Na replacement
  - Fe needs increased due to gastrointestinal blood loss and malabsorption especially if patient has loss of proximal small bowel


Liver Disease – Nutritional Considerations

Restricted nutrients

• Na
  – Administered in small amounts because excess Na intake in the face of hypoalbuminemia contributes to increased ascites
• Cu and Mn
  – If cholestasis is present
• Total fluids
  – Determined by weight and fluid balance
• If encephalopathy present, restrict protein intake and monitor serum ammonia. Use of branch chain containing protein products may be helpful e.g., TrophAmine®
• Adjustment in lipids need to be made in patients with hyperlipidemia

Nutrients requiring supplementation

• Protein: if hypoalbuminemia present
• Fat soluble vitamins D, E and K: if deficient
• Zn: if deficient
• K: if on diuretics

<table>
<thead>
<tr>
<th>Renal Disease – Considerations for use of PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peritoneal dialysis complicated by ileus or peritonitis</td>
</tr>
<tr>
<td>• Critically ill patients on hemodialysis</td>
</tr>
<tr>
<td>• Severe malnutrition, intolerance of enteral feeds</td>
</tr>
<tr>
<td>• Short bowel syndrome</td>
</tr>
<tr>
<td>• Intestinal obstruction (mechanical or pseudo-obstruction)</td>
</tr>
</tbody>
</table>

Use of PN may be considered in patients with renal disease who have the above conditions.
In patients with acute renal failure, fluid intake is often reduced and the amount of fluid available for PN significantly impacts on caloric intake. Protein intake is often restricted to meet minimum requirements. Electrolyte intake is based on serum levels. Once the patient goes on dialysis, fluid, caloric and protein intake can be increased to better meet needs.
Protein losses are increased in dialysis
Need to meet protein needs but can deal with urea through dialysis, i.e. don’t reduce protein requirements

Renal Disease – Fluid & Electrolyte Considerations

Restricted nutrients
- Total fluids – determined by dialysis settings
- Na, K, Phos (administered in small amounts because excretion is decreased)
- Deduct dialysate dextrose when calculating glucose infusion rate (GIR)
- Lipids in patients with hyperlipidemia of renal failure
- Limit vitamin C to <100 mg per day in patients with hyperoxaluria

Nutrients requiring supplementation
- Protein
  - Increased losses with dialysis
- Na and alkali
  - Increased losses in ‘nonoliguric’ renal failure
    (e.g., congenital hydronephrosis, renal dysplasia)
Oncology - Considerations for Use of PN

- Tumors causing gastrointestinal obstruction
- Severe malnutrition and intolerance of enteral feeds
- Uncontrolled nausea and vomiting
- Severe mucositis and enteritis (especially in stem cell transplant recipients)
- Typhlitis
- Post surgery
Use PN for a short period and then implement NG tube feeds. Type and amount of protein should be modified based on disease.

This slide reviews the basic principles of PN support in metabolic disease. The following slides will go over principles of management in select metabolic disorders.
Inborn Errors of Metabolism – Phenylketonuria

- Hypercatabolism occurs during stress
  - Parallels the extent of infection/injury
- Goal is prevention of prolonged phenylalanine (PHE) elevation
- Interventions to depress catabolic response
  - PN as bridge to enteral nutrition
  - PHE-free parenteral amino-acid solution with some standard parenteral amino-acids

Acosta PB. Nutrition Management of Patients with Inherited Metabolic Disorders- Chapter 5- Phenylketonuria p137.
<table>
<thead>
<tr>
<th>Inborn Errors of Metabolism</th>
<th>Mitochondrial Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avoid exposure to PN if possible</td>
<td></td>
</tr>
<tr>
<td>• High-glucose diet is a metabolic challenge for impaired oxidative phosphorylation</td>
<td></td>
</tr>
<tr>
<td>– Glucose oxidation is largely aerobic in the liver</td>
<td></td>
</tr>
<tr>
<td>• High lipid/low carbohydrate diet recommended in Complex I deficiency</td>
<td></td>
</tr>
<tr>
<td>• Carnitine supplementation is recommended in patients with secondary carnitine deficiency</td>
<td></td>
</tr>
</tbody>
</table>

Munnich A, Rötig A, Cormier-Daire V, et al. PART 10: DISORDERS OF MITOCHONDRIAL FUNCTION. Chapter 99: Clinical Presentation of Respiratory Chain Deficiency
Usual crises triggers include infections, fasting, exposure to intact protein loads (isoleucine, methionine, threonine, valine). Patients need a low-protein diet (0.5–1.5 g/kg per day) or selective reduction in the content of propionate precursors. Even though the goal is to minimize the number of attacks of ketoacidosis, one cannot prevent attached and normal development in all patients. One needs to minimize fasting because catabolism increases propionate metabolites.

Strategies employed during ketoacidosis include withdrawal of all dietary protein,
administer parenteral sodium bicarbonate, administration of parenteral glucose to avoid catabolism, and treatment of acute attacks accompanied by hyperammonemia treated with peritoneal dialysis.

**TPN has been used to treat critically ill patients and daily monitoring/adjustment of components based upon metabolic parameters is required. In one small series of longer term TPN use, protein intake was started at 0.5 grams/kg/day (propionyl CoA precursors were 0.07 mmol/kg/day), amino acid admixture was adjusted (lysine (diacetate) reduced by 50% to decrease acetate, alanine added to make up) and metabolic status was frequently monitored. This included reduction of glycine concentration reduced by 50% due to oxaluria and adjustment of propionyl precursors based upon metabolic status.**

**PART 9: ORGANIC ACIDS**

**Chapter 94: Disorders of Propionate and Methylmalonate Metabolism**

Wayne A. Fenton, Roy A. Gravel, David S. Rosenblatt

withdrawing all dietary protein and administering sodium bicarbonate parenterally; glucose is also required to avoid catabolism. Acute attacks, particularly those accompanied by hyperammonemia, have been treated with peritoneal dialysis. Total parenteral nutrition also has been used to treat critically ill patients.

Parenteral nutrition in propionic and methylmalonic acidemia

Stephen G. Kahler, MD, David S. Millington, PhD,
Stephen D. Cederbaum, MD, Jorge Vargas, MD, Laurel D. Bond, RD,
David A. Maltby, MS, Diane S. Gale, BS, and Charles R. Roe, MD(J PEDIATR 1989;115:235-41)

31-month-old with propionic acidemia: precursors of propionyl-CoA (isoleucine, valine, methionine, and threonine) were mixed separately from the other amino acids to facilitate dietary changes. In addition, an orally administered L-carnitine supplement, 50 mg (0.31 mmol)/kg every 6 hours, was maintained throughout the hospital stay to enhance the excretion of propionyl-CoA as propionylcarnitine; 3 and daily monitoring of metabolic status was carried out by analysis of urinary organic acids using a gas chromatography-mass spectrometry method to provide information on which dietary adjustments could be based.

In MSUD metabolic issues and toxicity are tied to plasma leucine status. There is little toxicity with increased levels of isoleucine or valine. L1 neutral transporter allows brain update of Paa, Trypt, Leu, Meth, Isol, tyr, hist, val, thr and in cases of leucinosis, leucine is taken up by the L1 transporter at the expense of other L-neutral amino acids especially in the brain. The sequela of BCAA deficiencies include poor growth, anemia, immunodeficiency, dysmyelination/global delays.


Inborn Errors of Metabolism
Glutaric Aciduria Type 1

- Acute crisis management to prevent encephalopathy
  - Eliminate dietary lysine, tryptophan and total protein for 48 hrs until reduction of organic acidemia
  - Management of infants
    - 10% dextrose and electrolytes 150 mL/kg per day (GI:R 10mg/kg/min)
    - Calorie goal: 120-150 kcal/kg per day
    - Lipids: 2 - 3 g/kg per day
    - Oral riboflavin 100 - 200 mg per day with food in 15 - 25 mg portions
  - After stabilized, introduce protein preferably through the enteral route
    - Parenteral protein
      - short term PN: 0.8 g/kg per day
      - long-term PN: use tailored protein solutions


This slide covers the aims of nutritional therapy in patients with urea cycle disorders. The goal should be to restrict nitrogen intake and minimize catabolism as well as activate pathways aside from urea for nitrogen excretion. Arginine, which is downstream in the pathway requires supplementation.

The risk factors for hyperammonemia are birth in neonates and illness, excess protein intake, surgery and catabolic stressors in older patients. Similar to other disorders, the plan is to stop catabolism through the delivery of high caloric intake of glucose and lipids with the addition of insulin if needed to stop the catabolism of glucose.

Home Parenteral Nutrition
Founded in 1983 by Lyn Howard, MD and her patient, Clarence "Oley" Oldenburg, the Oley Foundation is a national, independent, non-profit 501(c)(3) organization that provides information and psycho-social support to consumers of home parenteral and enteral nutrition, helping them live fuller, richer lives. The Foundation also serves as a resource for consumer's families, homePEN clinicians and industry representatives, and other interested parties. http://www.oley.org/

Home PN - Preparation for Discharge I

- Parents/caregivers have to be informed, motivated and able to cope with all medical, emotional and technical problems related to Home PN (HPN)
- Family suitability for HPN must be carefully assessed by a healthcare team member; may include
  - visiting the home and examining practical details such as space for dedicated refrigerator, electricity, and connected telephone
- The assistance of a social worker is needed before discharge especially if the home environment is inadequate

### Home PN - Preparation for Discharge I (cont’d)

<table>
<thead>
<tr>
<th>Parents Knowledge</th>
<th>Handling</th>
<th>Catheter &amp; Line</th>
<th>Pump</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Care</td>
<td>Hand washing technique</td>
<td>Flushing of heparinization initiation &amp; termination of infusion</td>
<td>Operation maintenance</td>
<td>Catheter exit site temperature</td>
</tr>
<tr>
<td></td>
<td>Preparation of sterile field</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Drawing up solutions into syringe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>Materials missing</td>
<td>Blockage of the line breakage/split catheter air in the line</td>
<td>Alarms exit site infection fever digestive problem</td>
<td></td>
</tr>
<tr>
<td>What to do?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Who to contact?</td>
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</tbody>
</table>

Parents/caregivers will be asked to add the multivitamins to the PN solution just prior to it being administered. Other additive that may need to be added include iron and ranitidine.
Home PN - Preparation for Discharge III

- Parents/caregivers also need to be taught to recognize common central venous catheter problems
  - Occlusion
  - Damage
  - Accidental removal
  - Infection e.g., fever

- They should be aware of whom to contact and how to provide first aid

- They should also be able to recognize and manage the symptoms of hypoglycemia and dehydration
The survival probabilities at 2, 5, 10, and 15 years were 97%, 89%, 81%, and 72%, respectively. Also the cause of death varied with diagnosis. In children that died from primary digestive disorders, 24% died from their primary disease and 48% died from liver disease or sepsis. In children that died from primary non-digestive diseases, 94% died from their primary disease and 6% died from liver disease or sepsis.


<table>
<thead>
<tr>
<th>Home PN – Five Year Prospective Study</th>
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</thead>
<tbody>
<tr>
<td>• The primary cause of death on HPN</td>
</tr>
<tr>
<td>– Underlying disease-related in patients with HPN duration ≤ 2 years</td>
</tr>
<tr>
<td>– HPN-related in those on HPN duration &gt;2 years</td>
</tr>
<tr>
<td>• For children, survival rate was</td>
</tr>
<tr>
<td>– 90.9% for those not transplant eligible (n=44)</td>
</tr>
<tr>
<td>– 90.7% for those eligible for transplant but not transplanted (n=43)</td>
</tr>
<tr>
<td>– 75.0% for those actually transplanted (n=12)</td>
</tr>
<tr>
<td>• Follow up period for those transplanted not clear</td>
</tr>
</tbody>
</table>
Home PN – Economics

- HPN is approximately 50-75% more “economical” than inpatient hospital care
- The longer a patient survives on HPN, the more cost-effective home treatment becomes.
- HPN in children in the UK led to cost savings of about 2 million Euros in a single year by decreasing the incidence of septic episodes (1/142 days in hospital to 1/567 days at home)


Home PN - Long-Term Adequacy

- Nutritional measurements are key to determining adequacy of the PN, patients should demonstrate adequate weight gain and linear growth
- Address developmental delays with appropriate interventions
The inserted growth chart is of a patient on home PN with acquired SBS due to surgical resection for Crohn’s disease. The first arrow indicates the start of PN. Because of good weight gain, PN was weaned. The second arrow indicates the restarting of PN.

EN support should be tailored based on the patient.


The above are suggested, however there may be variation in certain populations e.g. adult and adolescents.

Other tests which may be considered include:
- Venous pH: some centres may check
- Prealbumin: can be monitored
- PT/PTT: could be done

Consider measuring urine Na levels to assess adequacy of Na intake especially in patients with SBS and growth problems.
During PN initiation it is customary to follow serum electrolytes closely.

Trace elements
- Mn: follow whole blood levels although ideal may be a MRI of brain
- Zn: serum zinc is not an accurate marker of zinc deficiency
- Cu: serum copper and ceruloplasmin
- Se: serum or whole blood selenium
- Fe: hemoglobin, serum ferritin or iron, transferrin saturation

Fat-soluble vitamins
- Vitamin A: serum vitamin A

**Vitamin E: serum vitamin E : total lipid ratio**, levels are more accurate if compared with total lipid levels. In children with liver disease Horwitt et al found a ratio of mg vitamin E / g total serum lipids greater than 0.8 indicated adequate levels.
- Vitamin K adequacy: prothrombin time, PIVKAII
- Vitamin D: 25-hydroxy vitamin D; both 1,25-Dihydroxy- and 25-Hydroxy- vitamin D in renal disease

Some experts believe that carnitine status should only be measured in the neonate.
Patients at risk for renal disease should have GFR monitored.

Patients on chronic PN, especially HPN, are at risk for nephropathy. This may be related to subclinical renal damage from components of PN, cumulative drug toxicity from nephrotoxic antibiotics used to treat central line infections.


Need to differentiate between a central line infection and colonization. About 22% of all hubs are colonized with bacteria.

The recommendations are that the tubing for lipids be changed every 12-24 hours and the dextrose tubing be changed every 72 hours unless it is a 3-in-1 solution.

Home PN - Mechanical Complications

- Catheter-related
  - Pneumothorax
  - Hematoma
  - Hemothorax
  - Malposition
  - Venous and intracardiac thrombosis
  - Air embolism
  - Catheter blockage / migration
  - Transient arrhythmias, perforation of the heart
- Infusate-related
  - Extravasation into local tissues, pericardium, peritoneum, thorax, mediastinum, liver and scalp
Non-thrombotic occlusions are caused by calcium phosphate precipitates, medication precipitates, lipid residue, or mineral precipitates. Thrombotic catheter occlusions are usually treated with thrombolytics. The use of 0.1N hydrochloric acid is most effective for clearing catheter occlusions due to precipitation of calcium-phosphate. For catheter occlusions due to precipitates associated with medications in the high pH range such as tobramycin and phenytoin, sodium bicarbonate 1mEq/mL has been anecdotally reported to be effective. 70% ethanol is the most effective solvent to dissolve lipid residue. NaOH may be used to dissolve mineral precipitates.

Picture insert is of an occluded line.
Treatment considered decreasing IV fat emulsion, start EN if only trophic, wean PN or adjust PN components.

Ovchinsky N. conjugated bile acid as potential early markers of parenteral nutrition associated liver disease. JPEN 2010;34(5):472-473
Ursodeoxycholic acid often used but limited data on its effectiveness if given enterally.


Early referral to an transplant or intestinal rehabilitation program may allow for avoidance of a liver transplant.

Home PN - Special Considerations in SBS/Intestinal Failure

- For children on long-term PN with, or at risk for, developing PNALD
  - Consider limiting IVFE to 1g/kg per day IVFE for long-term PN for prevention/treatment of cholestasis
  - Evidence emerging for restriction of IVFE to prevent or treat PN associated cholestasis
  - Alternate lipid forms not commercially available in the US (e.g. fish oil, structured lipids and olive oil) are utilized for prevention and treatment of PN associated cholestasis

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This is a slide of a bone and the blue staining represents Al deposition.

The etiology of metabolic bone disease seen in patients on chronic PN is unclear and probably multifactorial. It may be related to altered vitamin D metabolism, Cu and vitamin K deficiency, and aluminum toxicity. Clinically patients present with bone pain (back pain) and pathologic fractures. Aluminum toxicity is known to occur in the
brain, bone and liver causing bone pain, metabolic bone disease, osteoporosis, patchy osteomalacia, reduced bone aposition and fracturing osteomalacia, encephalopathy and impaired neurological development. However Advenier et al showed in 10 children (av age 8 year) on PN for an average of 6.5 years, elevated aluminum levels with no associated symptoms.

Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the