

Micronutrients in Parenteral Nutrition

Praveen Goday MD CNSP

Associate Professor, Pediatric Gastroenterology

Medical College of Wisconsin

Director, Nutrition Support

Children's Hospital of Wisconsin

What is an essential trace element?

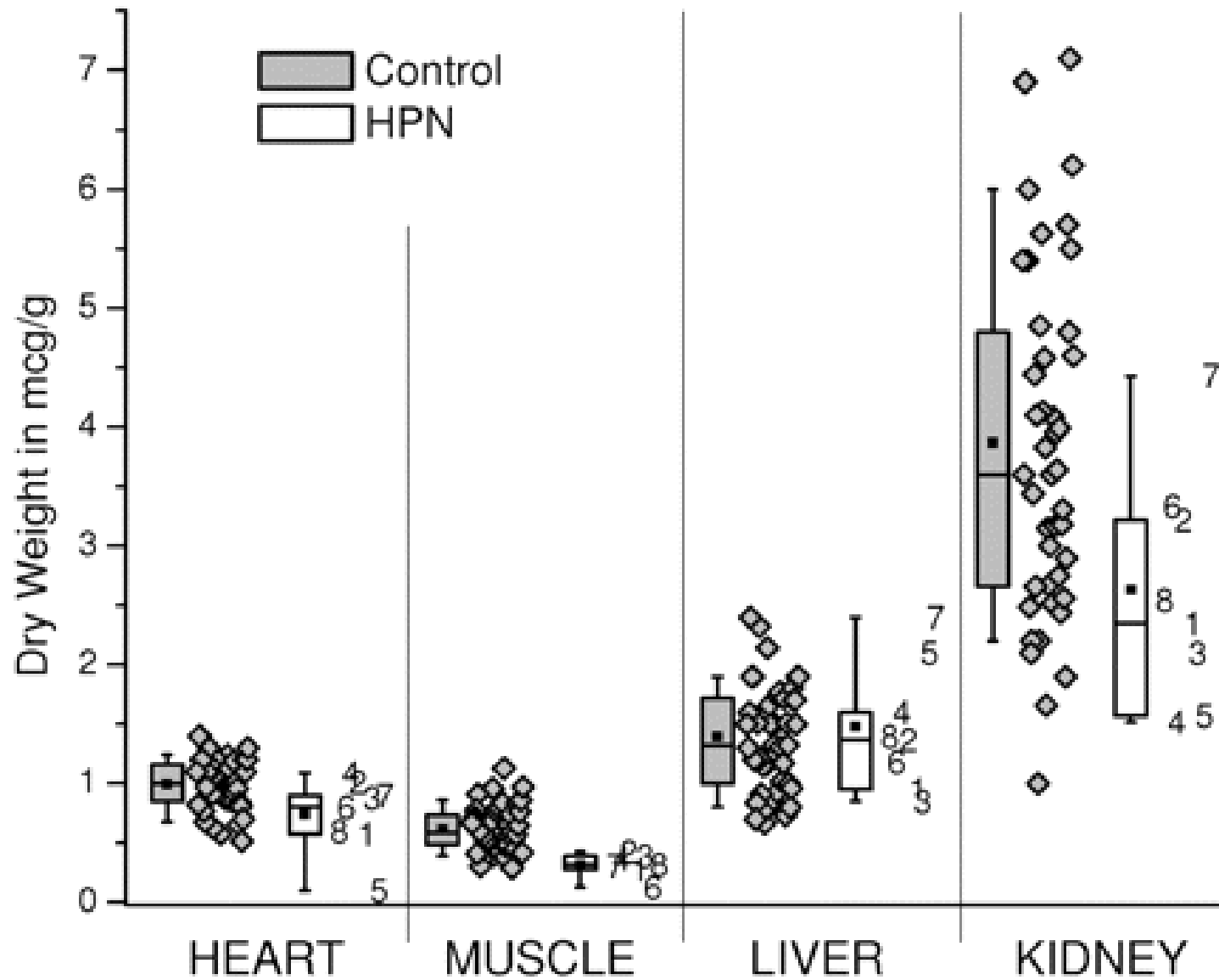
- Essential trace element
 - Present in healthy tissues of all living things
 - Constant tissue concentration
 - Withdrawal leads to reproducible functional abnormalities
 - Addition of the element prevents abnormalities
 - The biochemical change is prevented or cured with the clinical abnormality
- Using these criteria, 7 elements are necessary for human health
 - iron, zinc, copper, chromium, selenium, iodine, and cobalt (in vitamin B12)

The landmark Howard study

	Zn (mg)	Cu (mg)	Mn (ug)	Cr (ug)	Se (ug)
ASPEN 2004 recommendations	2.5 – 5	0.3-0.5	60-100	10-15	20-60
Multitrace 4	1	0.4	100	4	-
Multitrace 4 conc.	5	1	500	10	-
Multitrace 5	1	0.4	100	4	20
Multitrace 5 conc.	5	1	500	10	60
Abbott 4 Trace	4	1	800	10	-

F

SELENIUM



Howard study

- Iron and selenium
 - present at normal concentrations in all organs studied
- Zinc
 - occasionally elevated in kidney, and frequently elevated in liver
- Copper and Manganese
 - very elevated in liver and kidney, especially in those who died of liver disease
- Chromium
 - had a 10- to 100-fold higher than normal concentrations in nearly all tissues studied

	Zn (mg)	Cu (mg)	Mn (ug)	Cr (ug)	Se (ug)
ASPEN 2004 recommendations	2.5 – 5	0.3-0.5	60-100	10-15	20-60
Howard recommendations	3-6 mg	0.3-0.5	30-60	5-10	60-100

Additional zinc is necessary for intestinal losses

Stop ALT/ALKP >2 x normal. Check levels every 6-12 mo

Stop ALT/ALKP >2 x normal. Check levels every 6-12 mo

Zinc

Zinc

- In 1961, Prasad et al described a syndrome of hypogonadism, anemia, and stunting in humans who were geophagic
- Zinc supplementation
 - restored growth and sexual maturation

- Zinc is excreted mainly in the feces
- Diarrhea and stomal and fistula losses are the major sites of enhanced abnormal losses of zinc from endogenous sources in patients kept nil per os (NPO)

- There is no reliable way of assessing zinc status

- Currently, the best way of assessing zinc status and requirements is through multiple clinical parameters
- Abnormal gastrointestinal losses, hypercatabolism, or amino acid infusions raise the need for zinc
- The clinical syndrome of acrodermatitis enteropathica confirms the need for zinc supplementation.
 - scaly, red, desquamating lesions involving the nasolabial folds and hands. In severe cases it extends to the trunk, resulting in extensive exfoliation and secondary skin infection. There is often loss of hair.

Zinc

- Zinc is an essential trace element and must be added to all PN mixtures
- In patients without gastrointestinal losses, 3–4 mg should be given daily
- In patients with fistula, diarrhea, and intestinal drainage, 12 mg of zinc should be added for each liter of loss
- In patients with burns, addition of about 36 mg/d of zinc may reduce infectious complications

Copper

- Copper deficiency is rare
- Reported in prolonged severe malabsorption, premature infants, children recovering from severe malnutrition, and patients receiving PN without copper supplementation
- Manifestations
 - anemia (often hypochromic, microcytic), leukopenia, and a variety of bone abnormalities
 - ? marginal copper deficiency can result in cardiac diseases, arthritis, loss of hair pigmentation, and neurologic abnormalities, mimicking vitamin B12 deficiency

Cu toxicity

- Chronic copper toxicity
 - is illustrated in Wilson's disease
 - high levels of copper in liver, brain, kidney, and other organs
 - The disease is manifested as cirrhosis of the liver, a variety of neurologic disorders, and renal damage

Cu balance studies

- The biliary tract is the predominant route for copper excretion
 - Patients with cholestasis had decreased copper excretion through the gastrointestinal tract and tended to retain copper excessively
 - Patients with diarrhea have a need for additional copper

Copper

- Copper should be routinely prescribed to patients receiving PN
- The usual dosage of copper in PN is 0.3 mg/day for adults and 20 ug/kg/day for pediatric patients (not to exceed 0.3 mg/day).
- Patients with liver disease should receive a reduced dosage of 0.15 mg/day.
- Patients with persistent diarrhea or gastrointestinal fluid losses should receive between 0.4 and 0.5 mg/day.
- Copper requirements (as those of other nutrients) should be periodically reassessed and corrections made as needed
- Serum copper and ceruloplasmin levels should not be used as the sole indicators of copper requirements (the clinical circumstances should be a part of the assessment)

Iron

Iron

- Iron is an essential trace element
- Iron is probably an essential component for most if not all PN regimens
- The quantity of iron to be included should take account of predicted requirements and needs a calibrated response in growing children

Iron...

- The needs of menstruating, pregnant, and lactating women are greater than those of adult men
- Intravenous dose
 - 1 mg elemental iron per day in adult men and postmenopausal women
 - 1.5 mg/d in menstruating women
 - 2.0 mg/d for those who are in the later stages of pregnancy or lactating
- Continued monitoring of iron status is recommended

Stages of iron deficiency

- Stage 1 – loss of body stores
- Stage 2 – dyserythropoiesis in the bone marrow
- stage 3 – overt iron deficiency anemia

Lab markers of iron deficiency (ID)

- A ferritin level of $\leq 12\mu\text{g/L}$
 - is highly specific indicator for ID (98% specificity).
 - The sensitivity for this is only 25%
 - If a cut-off level of $30\mu\text{g/L}$ is used for ID diagnosis, sensitivity improves to 92%
- Other tests
 - Transferrin
 - Transferrin saturation
 - Transferrin receptor

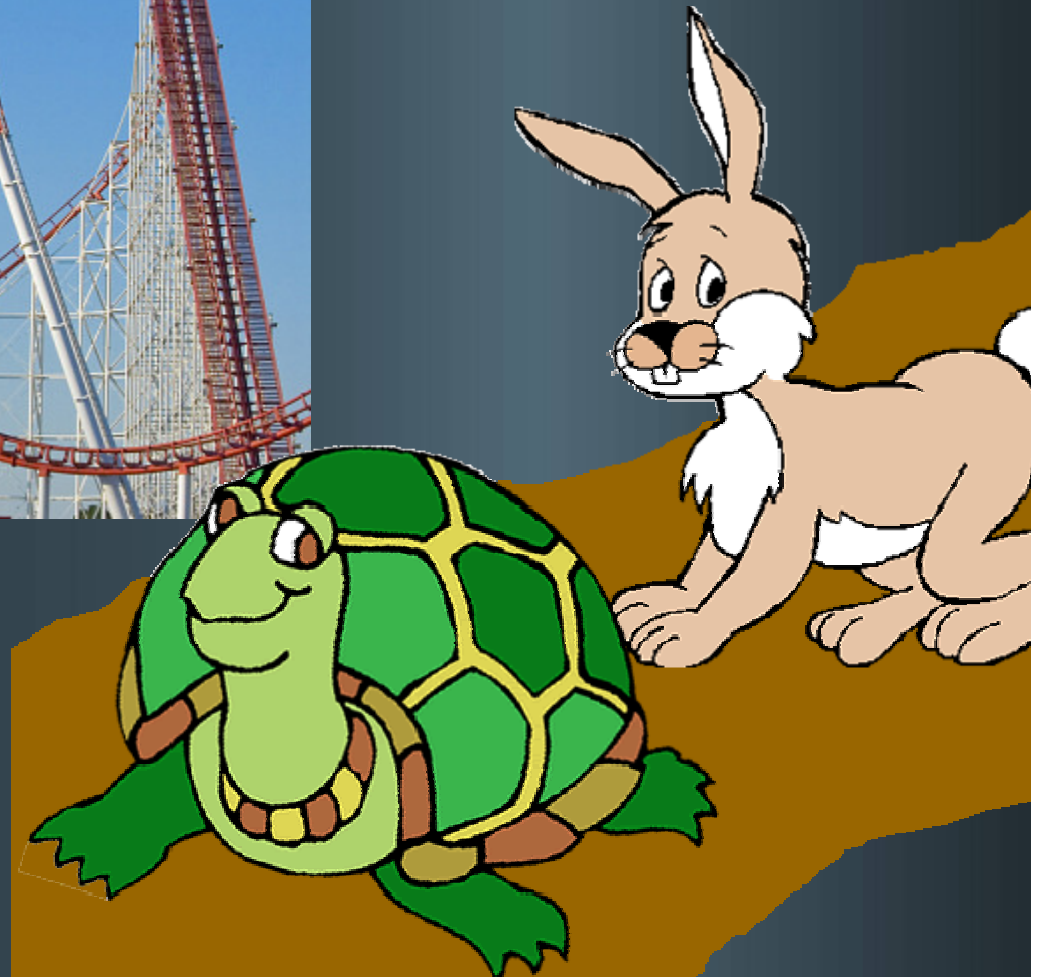
Iron and parenteral nutrition

- None of the trace element mixes contain iron
- Iron is incompatible with lipid (in three-in-one mixtures)

Considerations in intestinal failure

- Patients with short bowel syndrome may not tolerate oral Fe
- Since iron is excreted by shedding of the intestinal epithelium
 - patients with very short intestinal lengths may need smaller amounts of iron
 - patients with normal lengths of bowel that are dysfunctional/inflamed may need more iron as in radiation enteritis or Crohn's disease

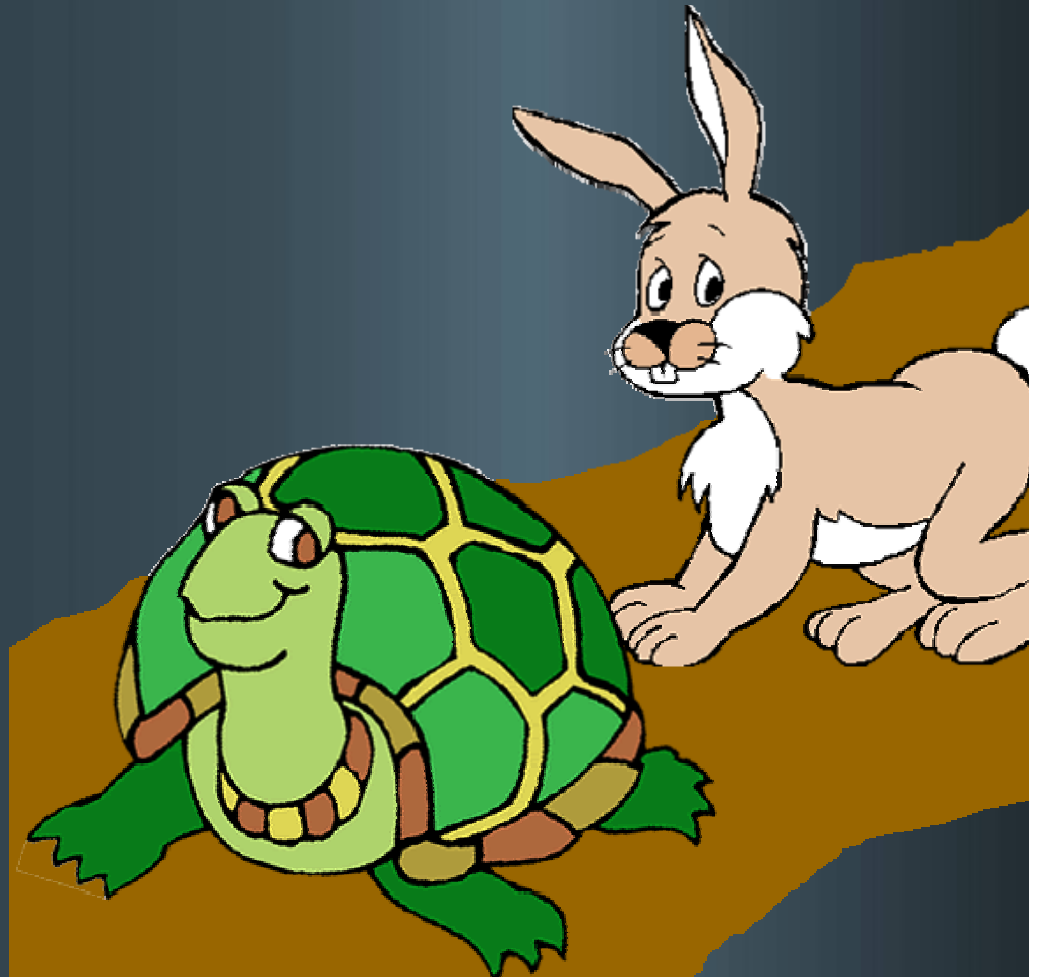
Methods of giving parenteral iron





Total iron deficit (mg) =
body weight (kg) X 0.24 X (target – actual
hemoglobin [g/L]) + 500

- Weekly dose of parenteral iron in bags that do not contain any lipid



Selenium

Selenium

- Selenium (Se) is required for synthesis of selenocysteine, now known as amino acid 21
- At least 25 selenoproteins exist in human tissues

Selenium

- Total plasma Se is the most widely used test of Se status
- In patients on TPN, this test is likely to be fairly accurate

Selenium deficiency

- Keshan disease
 - a cardiomyopathy in selenium-poor parts of China
- Se deficiency during PN
 - Fatal or reversible cardiomyopathy
 - skeletal muscle myopathy
 - abnormalities in nails and hair
 - macrocytic anemia

Se recommendations

- Selenium
 - should be provided to all PN patients
 - should be provided from the beginning
 - 60–100 ug/day will meet requirements in most patients
 - Patients who commence PN already depleted in selenium may require more

Se recommendations

- Good evidence that up to 400 ug/day is beneficial in burn patients
- Inconclusive regarding the benefit of high-dose selenium in severe sepsis
- Selenium status should be monitored by measurement of plasma Se together with a measure of systemic inflammation
 - ↑ CRP is associated with ↓ plasma Se

Chromium

Is chromium essential ?

- Serum Cr level is high in newborns and declines in adults
- If Cr were simply a contaminant, the amount of contamination in the body would increase with time

Is chromium essential ?

- Cr deficiency has been reported in adult women with massive bowel resection receiving parenteral nutrition
- All had glucose intolerance that was reversed by daily Cr supplementation in the PN solution

Is chromium essential ?

- Cr absorption is inversely proportional to intake in humans
- The fact that regulation of Cr absorption exists implies essentiality

- Hyperglycemia results in increased urinary Cr excretion

- Cr occurs as a component of metalloenzymes

Cr deficiency

- The only method for diagnosing Cr deficiency
 - demonstrating insulin resistance or an abnormal glucose clearance that improves after Cr supplementation and reappears after the supplement is withdrawn

What do we do with chromium?

- The concentrations of contaminating Cr in PN solutions seem to be high enough to prevent Cr deficiency
- These contaminants can increase the amount delivered by 10–100%
- However, changes in purification methods for PN solutions could lead to insufficient concentrations of Cr
- Serum Cr concentrations and glycosylated hemoglobin should be measured regularly in patients receiving long-term PN



Manganese

- Mn is considered to be an essential trace element
- Deficiency is virtually unknown in humans
- Excessive doses of Mn 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)

Manganese...

- Various TPN elements are contaminated with Mn
- The main pathway for Mn excretion is via the hepatobiliary system
- 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
 - These tests have to be obtained with the greatest deal of care

- There is now a persuasive argument for not routinely adding Mn to PN admixtures
 - In long-term PN patients, the intestinal regulatory mechanism for Mn is bypassed
 - Mn deficiency is virtually unknown in human beings
 - Neurotoxic damage from Mn toxicity is a major concern
 - Ubiquitous Mn contamination appreciably increases the actual amount delivered, and together with dietary sources could be sufficient to cover most PN requirements

- Routine whole-blood measurement of Mn in combination with cranial MRI is recommended to monitor potential accumulation
- Fixed-dose multiple trace element formulations restrict prescribing options and make it difficult to adjust Mn levels without reducing the other essential trace elements
- Manufacturers should reformulate these products with lower and/or zero Mn content and make individual trace elements available
- All PN products should be labeled with a maximum allowable trace element contamination level

Iodine

Iodine

- Commercially available products for enteral nutrition generally provide 75–110 ug iodine/serving
- Daily iodine requirements in adult patients receiving total enteral nutrition or TPN are estimated to be 70–150 ug
- Although most PN formulations do not contain iodine, deficiency is not likely to occur because of cutaneous absorption from iodine-containing disinfectants and other adventitious sources of iodine
- PN solutions may contain as much as 15–25 ug iodine as contaminant
- There are no reported stability or incompatibility problems when iodine additions are made to PN mixtures
- Iodine deficiency symptoms have not been reported with in-hospital intravenous nutrition support

Iodine

- It has been suggested that thyroidal iodine stores are often adequate to meet the needs of patients requiring TPN for 3 months
- In addition, many persons on long-term PN are able to eat and drink limited amounts and have a functioning duodenum and thus may absorb dietary iodine
- For these reasons, many experts do not recommend supplemental iodine routinely for subjects receiving TPN

- Randomized controlled trials of iodine supplementation are needed in extremely preterm and extremely low birthweight infants, the group at greatest risk of transient hypothyroxinemia, with clinically important outcomes, including respiratory morbidity and neurodevelopment.
- Iodine requirements for persons on long-term PN should be better defined, particularly when chlorhexidine-based antiseptics are used in place of iodinated antiseptics
- If it is shown that there is increased risk of iodine deficiency in such patients, the possible need for revision of current PN iodine guidelines should be considered

Miscellanea

Vitamins

Vitamin D

- Vitamin D is required by all PN patients as well as other human subjects
- It must be supplied in the PN solutions or by limited ultraviolet irradiation.
- Serum 25-OH-D levels should be monitored and kept in the range of 30–100 ng/ml
- Vitamin D may reduce the risk of
 - colorectal cancer, breast cancer, autoimmune diseases, and heart attacks

- The availability of parenteral vitamin D preparation should be strongly pursued to provide medical practitioners a means of achieving levels of 25-OH-D₃ that provide these benefits

Vitamin K

- Although a weekly intravenous supply of 250–500 ug phylloquinone is sufficient to maintain effective coagulation in most patients on PN, a daily injection of 150 ug phylloquinone should cover the requirements of all patients and will be also more effective in maintaining the γ -carboxylation status of noncoagulation Gla proteins
- Lipid emulsions provide a variable amount of phylloquinone according to the type of oil, and this source of vitamin K needs to be factored into requirement calculations
- Pregnant women present a special risk category because of the poor placental transport of vitamin K and consequent danger that even subclinical maternal vitamin K deficiency can result in severe bleeding or skeletal defects in the fetus
- PIVKA II is a better test of Vitamin K sufficiency

- The phylloquinone content of present PN formulations may cause vitamin K overload in premature infants
- Although anticoagulant control in patients taking vitamin K antagonists such as warfarin may be improved by a regular vitamin K intake, the current FDA recommendations for multivitamin preparation (150 ug/d) and variable amount from lipid emulsions (up to 400 ug/d) may cause warfarin resistance. Such high phylloquinone intakes are likely to completely negate any antithrombotic effects of low-dose (minidose) warfarin therapy

Carnitine

- Nutritional supplementation of carnitine should be 2–5 mg/kg/day and be administered via the route used for administration of macronutrients
- For instance, if 50% of the protein is administered parenterally, 50% of the carnitine should be administered parenterally
- Pharmacologic supplementation of carnitine should be 50–100 mg /kg/day should be reserved for the treatment of inborn errors of metabolism

Choline

- Choline may be able to partially treat or prevent PN-associated liver disease
- Choline as an injection is not currently available commercially for use in patients
- Available experimental data suggest an appropriate intake in adults would be 1–2 g of choline chloride daily
- No data are available for young children and infants