CLINICAL NUTRITION

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals

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A R T I C L E   I N F O

1. Methods

Literature Search
Timeframe: 2004 — 11/2014, in addition relevant earlier publications were considered.

Type of publications: randomized controlled studies; case-control or cohort studies; case reports; case series; expert opinion.

Key words: Parenteral Nutrition; Infusions, Parenteral; Trace Elements; Chromium; Copper; Iodine; Iron; Manganese; Molybdenum; Selenium; Zinc;

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Age: Child, infant, preterm
Language: English.

152 abstracts were found. Of these, 69 full text papers were assessed. In addition to the retrieved papers the authors found a few additional papers by hand search.

2. Iron

R 7.1	**In patients receiving PN, iron supplementation should preferentially be given enterally rather than parenterally, if tolerated. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.2	**Routine provision of iron in parenteral nutrition should not be given for short term PN (<3 weeks) (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.3	**Patients receiving long-term PN, who cannot maintain adequate iron status using enteral iron supplements, should receive parenteral iron supplementation. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.4	**Parenteral iron can be given daily added to PN solution or as intermittent, separate infusions. (GPP, conditional recommendation, strong consensus)**
R 7.5	**If given daily, and assuming no enteral iron supplementation, routine parenteral iron supplements should be given at a dose of 200−250 μg/kg/day in preterm infants and 50−100 μg/kg per day up to a maximum dose of 5 mg/day in infants and children. (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.6	**Even though currently no intravenous iron preparation is approved for pediatric use in Europe, iron sucrose is the most studied iron preparation in children, severe adverse events are rare and it is approved in the USA for use in children from 2 years of age. It is therefore recommended for intermittent infusions. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 7.7	**Iron status (at least ferritin and hemoglobin) should be monitored regularly in patients on long-term PN in order to prevent iron deficiency and iron overload. (LoE 4, RG 0, strong recommendation, strong consensus)**

Iron is an essential nutrient and iron deficiency results in anemia as well as poor neurodevelopment in children. However, iron is not routinely provided in pediatric parenteral nutrition (PN) mixtures and is usually not a component of commercially available trace element preparations. The major concern is that of iron overload. Parenteral administration of iron bypasses the homeostatic control of gastrointestinal iron absorption, causing loss of protection from iron overload if excessive quantities are provided, since humans have no mechanism for excretion of iron. Iron overload has been reported in children receiving prolonged PN and is associated with increased oxidative stress and increased risk of infections [1].

Thus, the enteral route of iron supplementation should always be preferred in patients receiving PN. Iron status (see below) should be monitored regularly in patients receiving long-term PN (>4 weeks) and parenteral iron supplementation should be initiated in those who cannot maintain adequate iron status on enteral iron supplements. There are two commonly used methods for delivering parenteral iron:

1. Addition of iron (e.g. iron dextran) to daily, fat-free PN solutions.
2. Intermittent iron infusions for iron repletion in anemic patients (e.g. iron sucrose).

A multitude of biomarkers are used to assess iron status, including both hematological (hemoglobin, mean cell volume, reticulocyte hemoglobin, protoporphyrin/heme ratio) and biochemical (ferritin, transferrin saturation, transferrin receptors). When screening for iron deficiency in children, the combination of ferritin and hemoglobin has a reasonably good sensitivity and specificity. In patients with chronic inflammation, transferrin receptors can be a useful addition since ferritin can be falsely elevated. Ferritin and transferrin saturation (the ratio between serum transferrin and serum iron) are useful for detection of iron overload.

Based on factorial calculations, parenteral iron requirements are estimated to be 200−250 μg/kg/day in preterm infants and 50−100 μg/kg per day in term infants and children [1,2] (see Table 1). Ongoing losses (e.g. gastrointestinal bleeding, frequent blood sampling) or increased demand (e.g. erythropoietin therapy) will increase iron requirements.

Adverse drug reactions associated with parenteral iron therapy are common. In various case series in adults, 2−5% of patients experience significant side effects. The processes leading to iron dextran induced symptoms are unclear, but include a type I (IgE-mediated) anaphylactic reaction which is caused by preformed dextran antibodies. Additional mechanisms include a type I anaphylactoid reaction that may be caused by transient overload of the transferrin binding capacity resulting in small amounts of free iron in the circulation (which appears to be dose related) and immune complex activation by specific IgG antibodies. Symptoms include dyspnea, wheezing, hypotension, nausea, vomiting, abdominal pain, arthralgia and myalgia. Most side effects are mild and self-limited with severe reactions occurring in a minority of patients and in conjunction with infusion of larger iron doses. An increased incidence of adverse effects has been reported in patients with collagen diseases. Despite previous episodes of allergic reactions, safe administration of iron dextran is possible following a pre-treatment protocol of methylprednisolone, diphenhydramine and ephedrine. While total dose infusions of iron dextran may be associated with allergic manifestations the administration of the standard maintenance doses may be well tolerated [1]. Low molecular weight dextran has less adverse effects than high molecular weight dextran [3]. More recently introduced iron compounds, e.g. iron sucrose, iron gluconate, iron carboxymaltose are considered to have less adverse effects than iron dextran.

There is a paucity of studies on the effects and complications of intravenous iron in children and, unfortunately, no intravenous iron product is currently approved for use in children in Europe. However, these products are nevertheless used in children. In the USA, iron sucrose is approved from 2 years of age and iron gluconate from 6 years of age for treatment of iron deficiency anemia in children with chronic renal disease. Other products used in children include iron dextran and iron carboxymaltose.

Most recent studies in children have been done using iron sucrose. In 6 studies, a total of 232 children received 1624 doses of iron sucrose and very few serious adverse reactions were observed [4−9]. In a randomized study of three different doses of iron sucrose (0.5 mg/kg, 1 mg/kg and 2 mg/kg) in 145 children, adolescents and young adults, no patient experienced an anaphylactic reaction and only one adverse event (skin rash) in a single patient was considered related to the study drug [4]. In one series of 38 children receiving a total of 510 doses of IV iron sucrose, there were 6 adverse reactions. The only significant reaction occurred in a patient receiving a dose which was greater than the recommended maximum dose of 300 mg [6]. In a case report, systemic iron toxicity with hepatocellular damage was observed in a pediatric patient receiving 16 mg/kg of iron sucrose [10].

There are a few studies on iron gluconate in children [11,12]. In one report, 23 children received a total of 216 doses of iron gluconate (0.75—1.5 mg/kg, maximum dose 125 mg). Only two adverse events were observed which were considered to be related to the treatment: one episode of pain and one episode of hypotension which did not require treatment [12].

There is only one published study of iron carboxymaltose in children [13]. In that study, 72 children with inflammatory bowel disease or other gastrointestinal diseases were given a total of 147 doses of ferric carboxymaltose [13]. The median dose was 500 mg and the maximum was 1000 mg. Only 3 mild adverse reactions were reported in that study.

Due to the higher risk of allergic reactions to iron dextran, it is recommended to give a test dose before the treatment dose. There are a few studies on low molecular weight iron dextran in children [14,15]. In the most recent one, 31 children received iron dextran at doses up to 1000 mg. In 5 patients, the iron dextran was discontinued due to adverse reactions.

Iron dextran at a concentration of 100 mg/L is stable up to 18 h at room temperature, and a concentration of 10 mg/L is stable for 48 h, when added to fat-free PN solutions [3]. Iron dextran cannot be added to lipid emulsions or all-in-one admixtures as it results in destabilisation of the emulsion. Ferrous citrate is also compatible with PN solutions, with no observed precipitation during infusion periods of 18—24 h [1]. Iron sucrose has been shown to be stable in fat-free PN solutions at concentrations up to 2.5 mg/L [16]. Iron chloride added to PN solutions is used in some institutions and may have advantages but studies are lacking.

In conclusion, due to the risk of iron overload and compounding difficulties, iron is not routinely added to pediatric PN solutions. On the other hand, intermittent iron infusions can be associated with adverse events. In long-term PN, iron status should be regularly monitored and if enteral iron supplementation is not sufficient to maintain adequate iron status, parenteral iron should be given, either added to PN (tested for stability) or as intermittent infusions.

3. Zinc

R 7.8	Zn should be provided with PN at a dose of 400—500 µg/kg/d in preterm infants, 250 µg/kg/d in infants from term to 3 months, 100 µg/kg per day for infants from 3 to 12 months and 50 µg/kg/d in children >12 months of age, up to a maximum of 5 mg/d for routine supplementation. (LoE 4, RG 0, strong recommendation, strong consensus)
R 7.9	Zn status (serum Zn, alkaline phosphatase) should be periodically monitored in patients on long-term PN and more often in those with high gastrointestinal fluid output (usually ileostomy losses), who may have significantly higher Zn requirements. (LoE 3, RG 0, strong recommendation, strong consensus)

Zinc (Zn) is an essential nutrient, involved in the metabolism of energy, proteins, carbohydrates, lipids and nucleic acids and is an essential element for tissue accretion.

Zinc deficiency is commonly reported in children on long term PN and is associated with stunted growth, risk of infections and a typical skin rash [2]. Children with increased enteral fluid losses are at especially high risk.

Urinary Zn excretion and enteral Zn losses occur in the parenterally fed infant [2]. Some amino-acids like histidine, threonine, and lysine have been shown to bind Zn increasing its renal ultrafilterability. Increased urinary losses of Zn and decreased plasma concentrations occur following thermal injury in children [1].

Premature infants need a higher Zn intake than term infants because of their rapid growth: 450—500 µg/kg per day to match in-utero accretion rate. Standard trace element preparations do not supply this amount, and additional Zn has to be added to PN fluid in the preterm infant, or those patients with high Zn losses e.g. from diarrhea, stoma losses or severe skin disease [1].

Current recommendations are to supply 400—500 µg/kg/d in preterm infants, 250 µg/kg/d in infants from term to 3 months, 100 µg/kg per day for infants from 3 to 12 months and 50 µg/kg/d in children >12 months of age (up to a maximum of 5 mg/d for routine supplementation [2,17] (see Table 1).

4. Copper

R 7.10	Cu should be provided with PN at a dose of 40 µg/kg/day in preterm infants and 20 µg/kg/day in term infants and children up to a maximum dose of 0.5 mg/d for routine supplementation.). (LoE 4, RG 0, strong recommendation, strong consensus)
R 7.11	Plasma Cu and ceruloplasmin should be monitored in patients on long term PN, especially if they develop PN associated liver disease or if they have high gastrointestinal fluid losses. (LoE 3, RG 0, conditional recommendation, strong consensus)

Copper (Cu), is an essential nutrient, and is a functional component of several enzymes, including cytochrome oxidase, superoxide dismutase, monoamine oxidase and lysyl oxidase.

Cu deficiency, which is associated with pancytopenia and osteoporosis, has occasionally been reported in children on long term PN [2].

Cu concentrations in plasma and cells as well as Cu metalloenzymes concentrations are indicative of Cu status [1]. Plasma concentrations of both Cu and ceruloplasmin, the major Cu transport protein, should be monitored during PN [1]. However, Cu-Zn superoxide dismutase (SOD) activity in erythrocytes seems to be a more sensitive indicator of Cu deficiency than plasma concentration of Cu or ceruloplasmin [1]. Other indicators of Cu status include neutrophil count (low in deficiency), SOD activity, platelet cytochrome-c oxidase activity and platelet Cu concentration [1].

Parenteral Cu requirements are estimated to be 40 µg/kg per day Cu for preterm infants and 20 µg/kg per day for term infants and children [2,18] (Table 1).

The high Cu content in gastrointestinal fluid means that losses should be balanced by a higher Cu intake (increased by 10—15 µg/kg) in PN. Plasma concentrations of total Cu and ceruloplasmin are invariably reduced in children with burns, so PN in these patients should be supplemented with more than 20 µg/kg Cu to avoid deficiency [1].

Cu is primarily excreted through bile, so it has previously been recommended to remove Cu from PN in patients with cholestasis. However, some recent data suggests that this is not necessary and may even cause Cu deficiency in children [19—21]. Nevertheless, Cu status should be monitored in patients with cholestasis.

5. Iodine

R 7.12	Iodine should be provided with PN at a daily dose of 1—10 µg/kg daily in preterms and at least 1 µg/kg/day in infants and children. (LoE 4, RG 0, strong recommendation, strong consensus)
R 7.13	Patients on long-term PN should be regularly monitored for iodine status by measuring at least thyroid hormone concentrations (LoE 4, RG 0, conditional recommendation, strong consensus)

Iodine is an essential component of the thyroid hormones thyroxin (T4) and tri-iodothyronine (T3), which are necessary for cellular metabolism and maintenance of metabolic rate. Thyroid function remained normal and serum iodine levels were not reduced in children receiving long-term PN without iodide supplementation, probably due to iodine contamination of the solutions, use of iodine-containing radiocontrast media, absorption of iodine present in the ingested food, and skin absorption of topical iodinated disinfectants [1].

It is often recommended that iodine should be provided with PN at a dose of at least 1 µg/kg daily (Table 1). However, iodine balance studies in preterm infants on PN indicated that a mean daily intake of 3 µg/kg/d was associated with negative iodine balance [22] and administration of 1 µg/kg/day of iodine in older children resulted in very low urinary iodine excretion (<50—100 µg/day), indicating a risk for iodine deficiency [23]. Hence the above stated minimum dose will result in iodine deficiency in long-term PN, if other sources of iodine are not administered.

Because recommendations for daily enteral iodine intake in preterm infants range from 10 to 55 µg/kg/d [24] and enteral iodine absorption is generally high, there have been recommendations to administer iodine at doses of 10—30 µg/kg/day in preterm infants with PN [2,22]. The dose of 30 µg/kg/day of iodine with PN is currently evaluated in an ongoing randomized controlled trial [25].

Iodine status is ideally monitored by iodine excretion in 24 h urine samples, which may be difficult to obtain. Normal thyroid function tests may be considered as surrogate markers for adequate iodine status.

6. Selenium

| R 7.14 | Se should be provided with PN at a dose of 7 µg/kg/day in preterms and 2—3 µg/kg/day in infants and children up to a maximum dose of 100 µg/day for routine supplementation. (LoE 4, RG 0, strong recommendation, strong consensus) |
| R 7.15 | Se status (plasma Se) should be monitored regularly in long term PN and in patients with renal failure. (LoE 4, RG 0, conditional recommendation, strong consensus) |

Selenium (Se) is an essential nutrient that acts mainly in antioxidant defense. Se is part of selenoenzymes and is an essential component of active glutathione peroxidase (GSHPx), an enzyme that may protect against oxidative tissue damage. Se deficiency, associated with low plasma Se, erythrocyte macrocytosis, depigmentation and muscle weakness, has been reported in children receiving long term PN without Se supplementation [2]. In adults, Se deficiency has been associated with hypertension, liver cirrhosis, osteopenia, immune disorders and carcinogenesis but causality has not been proven for any of these associations.

Se overload leads to selenosis in adults, characterized by headache, loss of hair and nails, skin rash, discoloration of teeth, paresthesia and paralysis. However there have been no reports of Se toxicity in children.

Dietary Se is highly bioavailable with an intestinal absorption of up to 80%. Se intake in breast-fed infants has been estimated to be 2.3 µg/kg per day [1,2].

Se status is usually monitored by measuring Se concentrations in serum or plasma and/or the activity of glutathione peroxidase (GSHPx) in plasma or red blood cells. Erythrocyte and platelet GSHPx activity are sensitive indices of Se status in PN patients [1], but in preterm infants, GSHPx activity is not a useful marker of Se status since it is affected also by immaturity and oxygen exposure.

Preterm babies are at high risk of oxidative injury (bronchopulmonary dysplasia [BPD], retinopathy of prematurity, white matter disease, particularly in the first days of life. In VLBW infants, plasma Se levels decrease during the first weeks of life [26]. Low Se status has been documented in pre-term infants and was associated with BPD [27].

Darlow et al. [28] performed a randomized, controlled, blinded trial of Se supplementation in 534 VLBW infants. Se dose was 5 µg/kg/day enterally or 7 µg/kg/day parenterally. A significant effect was observed on Se plasma concentrations, which reached similar levels as had been reported in healthy term infants.

We recommend a parenteral intake of 7 µg/kg/day in preterm infants, similar to the dose given in the Darlow study [28], allowing to reach Se status similar to that of term infants. In term infants and children, parenteral Se requirements are estimated to be 2—3 µg/kg/day, based on enteral requirements and high bioavailability [17,18] (Table 1).

7. Manganese

R 7.16	Mn should be supplied in long term PN at a dose of no more than 1 µg/kg/day (maximum of 50 µg/d for routine supplementation) (LoE 4, RG 0, conditional recommendation, strong consensus)
R 7.17	Blood Mn concentrations should be monitored regularly in patients on long term PN (LoE 4, RG 0, conditional recommendation, strong consensus)
R 7.18	If the patient develops cholestasis, blood concentrations of Mn should be determined and parenteral Mn should discontinued (LoE 3, RG 0, strong recommendation, strong consensus)

Manganese (Mn) is a cofactor for several enzymes including mitochondrial superoxide dismutase and pyruvate carboxylase and also activates other enzymes such as hydrolases, kinases and transferases. In animal models, Mn deficiency affects mucopolysaccharide and liposaccharide formation, and leads to impaired skeletal development and ataxia. High Mn intake during PN is probably one of several factors contributing to the pathogenesis of PN associated liver disease. It also causes a central catecholamine depletion state in the central nervous system, leading in adults to insomnia, headaches, anxiety, rapid eye movements, loss of coordination with a Parkinson-like disease [29]. Studies using magnetic resonance images (MRI) have reported high-intensity areas in basal ganglia, thalamus, brainstem and cerebellum due to Mn intoxication with disappearance of symptoms and MRI abnormalities after withdrawal of Mn administration [30]. Mn should, therefore, be carefully administered, particularly in patients receiving long-term PN. As central nervous system deposition of Mn can occur without symptoms, regular monitoring of Mn blood concentrations should be performed in children on long term PN. Taking into account the hazards of high Mn levels in children receiving long-term PN, a low dose regimen of no more than 1.0 µg (0.018 mmol)/kg per day (maximum of 50 µg/d for children) is recommended together with regular neurological examinations (Table 1).

8. Molybdenum

| R 7.19 | Molybdenum should be provided in long term PN at a dose of 1 µg/kg per day in LBW infants and 0.25 µg/kg per day (up to a maximum of 5.0 µg/day) in infants and children. (LoE 4, RG 0, conditional recommendation, strong consensus) |

Molybdenum (Mo) is essential for several enzymes involved in the metabolism of DNA. It is required by 3 enzymatic systems: xanthine dehydrogenase/oxidase, aldehyde oxidase, and sulfite oxidase. Mo deficiency may lead to cardiac and neurologic symptoms, in particular tachycardia and coma, together with high blood concentrations of sulfite and urate. To our knowledge there are no reports of Mo deficiency in infants. However, low-birth-weight infants (LBW) might be at particular risk for Mo deficiency. There are no toxicity data available in humans. In animals, Mo intoxication may cause diarrhea, impaired growth, infertility, gout, and may affect lung, kidney and liver function. Excess of Mo may interfere with Cu metabolism. There is no need for Mo during short term PN. However, in long term PN (>4 weeks), an intravenous intake of 1 mcg/kg per day (0.01 mmol/kg per day) seems to be adequate and is recommended for the LBW infant [1]. A daily parenteral intake of 0.25 μg/kg per day is recommended for infants and children (to a maximum of 5.0 μg/day) [1] (Table 1).

9. Chromium

R 7.20	Cr contaminates PN solutions to a degree that satisfies requirements; therefore, additional supplementation of Cr is considered unnecessary and Cr intake from PN should not exceed 5 μg/day. (GPP, conditional recommendation, strong consensus)

Chromium (Cr) is believed to be an essential micronutrient required for carbohydrate metabolism. There are no reported cases of Cr deficiency in children. The main concern of Cr in PN is the risk of Cr contamination of PN components. Deficiencies as well as increased serum Cr level have been described in patients receiving long-term PN. High serum Cr competes with iron for binding to transferrin and, hence negatively interferes with iron metabolism and storage. A daily intake of 0.2 μg/kg per day has been recommended for infants and children (maximum of 5 μg/day) receiving PN, although there is some evidence that lower intakes would be adequate. Supplementation is unnecessary since Cr contaminates PN solutions to a degree that satisfies requirements [1] (See Table 1).

Table 1
Estimated parenteral requirements of iron and trace minerals (μg/kg/d).

Mineral	Preterm	0–3 mo	3–12 mo	1–18 y	Max dose
Iron	200–250	50–100	50–100	50–100	5 mg/d
Zinc	400–500	250	100	50	5 mg/d
Copper	40	20	20	20	0,5 mg/d
Iodine	1–10	1	1	1	
Selenium	7	2–3	2–3	2–3	100 μg/d
Manganese	≤1	≤1	≤1	≤1	50 μg/d
Molybdenum	1	0.25	0.25	0.25	5 μg/d
Chromium	–	–	–	–	5 μg/d

Conflict of interest

None declared.

Appendix

Table: List of recommendations for iron and trace minerals

R 7.1	In patients receiving PN, iron supplementation should preferentially be given enterally rather than parenterally, if tolerated. (LoE 4, RG 0, strong recommendation)
R 7.2	Routine provision of iron in parenteral nutrition should not be given for short term PN (<3 weeks) (LoE 4, RG 0, conditional recommendation)
R 7.3	Patients receiving long-term PN, who cannot maintain adequate iron status using enteral iron supplements, should receive parenteral iron supplementation. (LoE 4, RG 0, strong recommendation)
R 7.4	Parenteral iron can be given daily added to PN solution or as intermittent, separate infusions. (GPP, conditional recommendation)
R 7.5	If given daily, and assuming no enteral iron supplementation, routine parenteral iron supplements should be given at a dose of 200–250 μg/kg/day in preterm infants and 50–100 μg/kg per day up to a maximum dose of 5 mg/day in infants and children. (LoE 4, RG 0, conditional recommendation)
R 7.6	Even though currently no intravenous iron preparation is approved for pediatric use in Europe, iron sucrose is the most studied iron preparation in children, severe adverse events are rare and it is approved in the USA for use in children from 2 years of age. It is therefore recommended for intermittent infusions. (LoE 3, RG 0, strong recommendation)
R 7.7	Iron status (at least ferritin and hemoglobin) should be monitored regularly in patients on long-term PN in order to prevent iron deficiency and iron overload. (LoE 4, RG 0, strong recommendation)
R 7.8	Zn should be provided with PN at a dose of 400–500 μg/kg/d in preterm infants, 250 μg/kg/d in infants from term to 3 months, 100 μg/kg per day for infants from 3 to 12 months and 50 μg/kg/d in children >12 months of age, up to a maximum of 5 mg/d for routine supplementation. (LoE 4, RG 0, strong recommendation)
R 7.9	Zn status (serum Zn, alkaline phosphatase) should be periodically monitored in patients on long-term PN and more often in those with high gastrointestinal fluid output (usually ileostomy losses), who may have significantly higher Zn requirements. (LoE 3, RG 0, strong recommendation)
R 7.10	Cu should be provided with PN at a dose of 40 μg/kg/day in preterm infants and 20 μg/kg/day in term infants and children up to a maximum dose of 0.5 mg/d for routine supplementation.). (LoE 4, RG 0, strong recommendation)
R 7.11	Plasma Cu and ceruloplasmin should be monitored in patients on long term PN, especially if they develop PN associated liver disease or if they have high gastrointestinal fluid losses. (LoE 3, RG 0, conditional recommendation)
R 7.12	Iodine should be provided with PN at a daily dose of 1–10 μg/kg daily in preterms and at least 1 μg/kg/day in infants and children. (LoE 4, RG 0, strong recommendation)
R 7.13	Patients on long-term PN should be regularly monitored for iodine status by measuring at least thyroid hormone concentrations (LoE 4, RG 0, conditional recommendation)
R 7.14	Se should be provided with PN at a dose of 7 μg/kg/day in preterms and 2–3 μg/kg/day in infants and children up to a maximum dose of 100 μg/day for routine supplementation. (LoE 4, RG 0, strong recommendation)
R 7.15	Se status (plasma Se) should be monitored regularly in long term PN and in patients with renal failure. (LoE 4, RG 0, conditional recommendation)
R 7.16	Mn should be supplied in long term PN at a dose of no more than 1 μg/kg/day (maximum of 50 μg/d for routine supplementation) (LoE 4, RG 0, conditional recommendation)
R 7.17	Blood Mn concentrations should be monitored regularly in patients on long term PN (LoE 4, RG 0, conditional recommendation)
R 7.18	If the patient develops cholestasis, blood concentrations of Mn should be determined and parenteral Mn should discontinued (LoE 3, RG 0, strong recommendation)

(*continued*)

| R 7.19 | Molybdenum should be provided in long term PN at a dose of 1 µg/kg per day in LBW infants and 0.25 µg/kg per day (up to a maximum of 5.0 µg/day) in infants and children. (LoE 4, RG 0, conditional recommendation) |
| R 7.20 | Cr contaminates PN solutions to a degree that satisfies requirements; therefore, additional supplementation of Cr is considered unnecessary and Cr intake from PN should not exceed 5 µg/day. (GPP, conditional recommendation) |

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