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Parenteral Nutrition Trace Element Product Shortage Considerations

ASPEN has developed shortage recommendations to assist members and other clinicians in coping with parenteral nutrition (PN) shortages for their patients.

For the most up-to-date product shortage information, see these websites:

- American Society of Health-System Pharmacists (ASHP), Drug Shortages Resource Center
- U.S. FDA Drug Shortages
- ASPEN Latest News and ASPEN Product Shortage Latest News

Important Note: These recommendations do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, the primary component of quality medical care is the result of the professional judgment of the healthcare professionals providing care. The information presented here is not a substitute or replacement for the exercise of professional judgment by healthcare professionals; rather, it is intended to supplement professional training and judgment. Circumstances and patient specifics in clinical settings may require actions different from those recommended in this document; in those cases, the judgment of the treating professionals should prevail. Use of this information does not in any way guarantee any specific benefit in outcome or survival.

These shortage recommendations are intended only for use during product shortages, when adequate product is unavailable. These measures are not ideal for ensuring safe and optimal patient care and should not be considered standard practice. Any deviation from manufacturer-recommended practices should be temporary and reversed once adequate product supply is restored. No single strategy will work for all organizations. Institutions must carefully evaluate each option, weighing potential risks and benefits before implementation. These recommendations are provided with the understanding that they are followed at the institution's own risk, and each organization assumes responsibility for any resulting outcomes.

Questions regarding these recommendations should be directed to clinicalpractice@nutritioncare.org.

Considerations for PN Trace Element Product Shortages

During the shortage period, consider one or more of the following measures:

1. Assess and routinely reassess each patient as to the indication for PN and provide nutrition via the oral or enteral route when possible.
2. Consider switching to oral or enterally administered multivitamin/multi-mineral/multi-trace element supplement products when oral/enteral intake is initiated (excluding patients with malabsorption syndromes). Supplements may not have a full spectrum of trace elements nor contain a daily enteral maintenance dose. Oral dietary supplements, including over the counter vitamin and mineral products, are not regulated by the U.S. FDA and therefore are not evaluated for purity, efficacy or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection.
3. Reserve intravenous trace elements for those patients receiving solely PN-dependent or those with a therapeutic medical need for intravenous trace elements.
4. If intravenous multi-trace element products are no longer available, administer individual parenteral trace element entities. Dosing guidelines for individual trace elements can be found in the 2012

A.S.P.E.N. position paper Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products.[1]

5. Purchase only as much supply as needed. In the interest of patient safety and fair allocation to all patients nationally, please do not stockpile.
6. During prolonged shortages of intravenous trace element products, the FDA may approve the temporary importation of alternative products. These products may have different trace element entities, ratios (doses), packaging and labeling than United States products. The Dear Healthcare Professional Letter accompanying imported products should be read carefully.
7. Compound PN in a single, central location (either in a centralized pharmacy or as outsourced preparation) in order to decrease inventory waste. Consider a supply outreach to other facilities in your geographic location.
8. Facilities and practitioners need to continue to observe and be compliant with the product labeling (e.g., package insert), USP General Chapter <797> Pharmaceutical Compounding-Sterile Preparations, and state Boards of Pharmacy and federal rules and regulations.
9. Include PN component shortages and outages in the health care organization's strategies and procedures for managing medication shortages and outages. These procedures should include:
    - a process to identify and monitor patients who receive no intravenous multi-trace elements or individual trace element entities,
    - a process to notify providers when this situation occurs, and
    - a process to notify patients receiving long-term (e.g. more than 1 month) PN therapy when their PN formulation has been adjusted for shortages and outages of PN components.
10. Observe for deficiencies when your institution is experiencing ongoing shortages. Increase your awareness and assessment for signs and symptoms of trace element deficiencies. Monitor serum trace element concentrations or other appropriate serum biochemical markers to evaluate trace element status.[1-4]
11. Report severe drug product shortage information to the FDA Drug Shortage Program (DSP).
12. Report any patient adverse events or medication hazard related to shortages to ISMP Medication Errors Reporting Program (MERP).

Considerations for a Shortage of Intravenous ADULT Multi-Trace Element Products

1. The use of intravenous Pediatric and Neonatal intravenous (IV) multi-trace element products for adults is strongly discouraged. Using pediatric or neonatal IV multi-trace elements for adults may contribute to a shortage of pediatric and/or neonatal products. A shortage of pediatric or neonatal IV trace-elements could create a potential risk of trace element deficiencies in neonatal and pediatric patients who may have an even greater need for trace elements. Furthermore, pediatric and neonatal IV multi-trace elements contain trace elements in doses or ratios that may be unsuitable for adults. Use caution and carefully review formulations if using IV neonatal multi-trace element products in pediatric patients.
2. When all options to obtain intravenous Adult multi-trace element products have been exhausted, ration intravenous Adult multi-trace element products in PN, such as reducing the daily dose by 50% or giving one multi-trace element product infusion three times a week.
3. Withhold intravenous Adult multi-trace element products from adult patients receiving partial enteral/parenteral nutrition or who can tolerate oral/enteral supplements. Consider withholding

intravenous Adult multi-trace element products for the first month of therapy to newly-initiated adolescent and adult PN patients who are not critically ill nor have preexisting deficits.

Considerations for a Shortage of PEDIATRIC and/or NEONATAL Intravenous Multi-Trace Element Products

1. Reserve Neonatal intravenous multi-trace element products for neonatal patients.
2. Reserve Pediatric intravenous multi-trace element products for pediatric patients.
3. The routine use of intravenous Adult multi-trace element products in pediatric and neonatal patients is not recommended.
4. Use the full dose of intravenous Adult multi-trace element product for children greater than 5 years of age. (Refer to the Adult IV multi-trace element shortage recommendations in the event of a concurrent shortage.)

Considerations for Managing Shortages of INDIVIDUAL intravenous Trace Element Entities

Consider one or more of the following measures for managing shortages of INDIVIDUAL intravenous trace element entities and their related signs and symptoms of deficiencies:

IV Zinc Shortage

1. Use oral/enteral supplementation if possible. Oral dietary supplements, including over the counter products containing trace elements, are not regulated by the U.S. FDA and therefore are not evaluated for purity, efficacy or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection. Note that oral/enteral zinc supplementation increases the expression of metallothionein in the enterocytes which can decrease the oral absorption of copper and may result in copper deficiency.
2. For general information on zinc see the 2012 A.S.P.E.N. position paper on Recommendations for Changes in Commercially Available Parenteral Multivitamins and Multi-Trace Element Products.[1]
3. Signs and symptoms of zinc deficiency: Dermatitis (skin rash of face, groin, buttocks, hands and feet) alopecia, non-healing ulcers, anorexia, low birth weight, growth failure, delayed sexual development, diarrhea, reduced taste and smell sensitivity, poor night vision, impaired cognitive function, recurrent infections, immune compromise, and impaired wound healing.[1,2,4-6]
4. Recent papers on zinc deficiency associated with PN component shortages are listed below:
    - Palm E, Dotson B. Copper and zinc deficiency in a patient receiving long-term parenteral nutrition during a shortage of parenteral trace element products. *JPEN J Parenter Enteral Nutr.* 2015;39:986-989.
    - Centers for Disease Control and Prevention. Notes from the field: zinc deficiency dermatitis in cholestatic extremely premature infants after a nationwide shortage of injectable zinc—Washington, DC, December 2012 [published correction appears in *MMWR Morb Mortal Wkly Rep.* 2013 Mar; 1562(10):196]. *MMWR Morb Mortal Wkly Rep.* 2013 Feb 22;62(7):136-137.
    - Ruktanonchai D, Lowe, M, Norton SA, et al. Zinc deficiency-associated dermatitis in infants during a nationwide shortage of injectable zinc - Washington, DC, and Houston, Texas, 2012-2013. [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2014 Jan 31;63(4):82]. *MMWR Morb Mortal Wkly Rep.* 2014 Jan 17;63(2):35-37.

- Franck AJ. Zinc deficiency in a parenteral nutrition–dependent patient during a parenteral trace element product shortage. *JPEN J Parenter Enteral Nutr.* 2014; 38:637-639.
- Sant VR, Arnell TD, Seres DS. Zinc deficiency with dermatitis in a parenteral nutrition dependent patient due to national shortage of trace elements. *JPEN J Parenter Enteral Nutr.* 2016;40:592-595.
- Maskarinec SA, Fowler VG. Persistent rash in a patient receiving total parenteral nutrition. *J Amer Med Assoc.* 2016;315:2223-2224.

IV Copper Shortage

1. Use oral/enteral supplementation if possible. Oral dietary supplements, including over the counter products containing trace elements, are not regulated by the U.S. FDA and therefore are not evaluated for purity, efficacy or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection. Note that oral/enteral zinc supplementation increases the expression of metallothionein in the enterocytes which can decrease the oral absorption of copper and may result in copper deficiency.
2. For general information on copper see the 2012 A.S.P.E.N. position paper on Recommendations for Changes in Commercially Available Parenteral Multivitamins and Multi-Trace Element Products.[1]
3. Signs and symptoms of copper deficiency: Hypochromic, microcytic anemia, leukopenia and neutropenia are common findings. Hypercholesterolemia may be observed. Children may exhibit skeletal demineralization (osteopenia). In premature infants signs may include depigmentation of hair and skin, aortic aneurysm associated with impaired elastin formation, neurologic dysfunction, and hypotonia.[1,2,7] Myopathy, neuropathy and myeloneuropathy have been reported in copper-deficient adults.
4. Recent papers on copper deficiency associated with PN component shortages are listed below:

- Pramyothin P, Kim DW, Young LS, Wichabnsawakun S, Apovian CM. Anemia and leukopenia in a long-term parenteral nutrition patient during a shortage of parenteral trace element products in the united states. *JPEN J Parenter Enteral Nutr.* 2013;37; 425-429.
- Palm E, Dotson B. Copper and zinc deficiency in a patient receiving long-term parenteral nutrition during a shortage of parenteral trace element products. *JPEN J Parenter Enteral Nutr.* 2015;39:986-989.

IV Chromium Shortage

1. No need to supplement (during shortage) unless signs and symptoms of clinical deficiency. Deficiency is rare. Chromium is present as a contaminant in other PN components. When a clinical deficiency is identified use oral/enteral supplementation if possible. Oral dietary supplements, including over the counter products containing trace elements, are not regulated by the U.S. FDA and therefore are not evaluated for purity, efficacy or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection.
2. For general information on chromium see the 2012 A.S.P.E.N. position paper on Recommendations for Changes in Commercially Available Parenteral Multivitamins and Multi-Trace Element Products.[1]
3. Signs and symptoms of chromium deficiency: Glucose intolerance refractory to insulin, hyperlipidemia, elevated plasma free fatty acids, weight loss, peripheral neuropathy, and encephalopathy.[1,2,8]

IV Manganese Shortage

1. No need to supplement (during shortage) unless signs and symptoms of clinical deficiency. Deficiency is rare. Manganese is present as a contaminant in other PN components. When a clinical deficiency is identified use oral/enteral supplementation if possible. Oral dietary supplements, including over the counter products containing trace elements, are not regulated by the U.S. FDA and therefore are not evaluated for purity, bioavailability or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection.
2. For general information on manganese see the 2012 A.S.P.E.N. position paper on Recommendations for Changes in Commercially Available Parenteral Multivitamins and Multi-trace Element Products.[1]
3. Signs and symptoms of manganese deficiency: Weight loss, transient dermatitis, ataxia and occasionally nausea and vomiting. In animals, manganese deficiency has been shown to affect reproductive function, and carbohydrate metabolism.[1,2,9]

IV Selenium Shortage

1. Use oral/enteral supplementation if possible. Oral dietary supplements, including over the counter products containing trace elements, are not regulated by the U.S. FDA and therefore are not evaluated for purity, efficacy or safety. The bioavailability of orally administered micronutrients is generally lower than that after intravenous administration. Bioavailability also varies depending on the salt form. Consult a pharmacist for product information and selection.
2. For general information on selenium see the 2012 A.S.P.E.N. position paper on Recommendations for Changes in Commercially Available Parenteral Multivitamins and Multi-Trace Element Products.[1]
3. Signs and symptoms of selenium deficiency: Deficiency usually takes years to develop. Symptoms include cardiomyopathy, myalgias, myositis, anemia, hemolysis, and impaired cellular immunity. Keshan disease is an endemic cardiomyopathy associated with selenium deficiency in China.[1,2,10]
4. Recent papers on selenium deficiency associated with PN component shortages are listed below:
    - Davis, C, Javid PJ, Horslen S. Selenium deficiency in pediatric patients with intestinal failure as a consequence of drug shortage. *JPEN J Parenter Enteral Nutr.* 2014;38:15- 118.

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2. Jensen GL and Binkley J. Clinical manifestations of nutrient deficiency. *JPEN J Parenter Enteral Nutr.*2002;26:S29-S33.
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8. Moukarzel A. Chromium in parenteral nutrition: too little or too much? *Gastroenterology*. 2009;137:S18-S28.
9. Hardy G. Manganese in parenteral nutrition: who, when, and why should we supplement? *Gastroenterology*. 2009;137:S29-S35.
10. Shenkin A. Selenium in intravenous nutrition. *Gastroenterology*. 2009;137:S61-S69.

Suggested Readings

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About ASPEN

The American Society for Parenteral and Enteral Nutrition (ASPEN) is dedicated to improving patient care by advancing the science and practice of nutrition support therapy and metabolism. Founded in 1976, ASPEN is an interdisciplinary organization whose members are involved in the provision of clinical nutrition therapies, including parenteral and enteral nutrition. With members from around the world, ASPEN is a community of dietitians, nurses, nurse practitioners, pharmacists, physicians, PAs, researchers, scientists, and students from every facet of nutrition support clinical practice, research, and education. For more information about ASPEN, please visit www.nutritioncare.org.