Multiple Micronutrient Deficiencies among Patients with Intestinal Failure during and after Transition to Enteral Nutrition

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Objectives To determine the prevalence of deficiencies of specific micronutrients (iron, zinc, magnesium, phosphorus, selenium, copper, folate, and vitamins A, D, E, and B12) in children with intestinal failure (IF), and to identify risk factors associated with developing these deficiencies.

Study design This study was a retrospective review of prospectively collected data from 178 children with IF managed by the Intestinal Care Center of Cincinnati Children's Hospital Medical Center between August 1, 2007, and July 31, 2012. Transition to full enteral nutrition (FEN) was defined as the period during which the patient received between 20% and 100% of estimated required nutrition enterally. FEN was defined as the patient's ability to tolerate 100% estimated required nutrition enterally for >2 weeks.

Results Necrotizing enterocolitis was the most common cause of IF (27.5%). Iron was the most common micronutrient deficiency identified both during (83.9%) and after (61%) successful transition to FEN, with a significant reduction in the percentage of patients with iron deficiency between these 2 periods ($P = .003$). Predictors of micronutrient deficiency after successful transition to FEN included birth weight ($P = .03$), weight percentile ($P = .02$), height percentile ($P = .04$), and duration of parenteral nutrition (PN) ($P = .013$). After multivariate adjustments, only duration of PN remained statistically significant ($P = .03$).

Conclusion Micronutrient deficiencies persist in patients with IF during and after transition to FEN. These data support the need for routine monitoring and supplementation of these patients, especially those on prolonged PN. *(J Pediatr 2013;163:1692-6)*.

Intestinal failure (IF) is defined as intestinal dysfunction of sufficient severity to mandate chronic dependence on parenteral nutrition (PN) for adequate growth, hydration, or micronutrient balance.[1] Normally, more than 95% of vitamins and minerals in food are absorbed in the proximal small bowel; an exception is vitamin B12, which is bound to intrinsic factor and absorbed in the terminal ileum.[2] Specific regions of the small intestine may be resected in some gastrointestinal disorders, resulting in both loss of bowel and malabsorption. In children with IF, the risk of developing nutrient deficiencies depends on the postsurgical anatomy, amount of bowel resected, and degree of malabsorption.[3] In addition, increased inflammation from bacterial overgrowth, impaired motility, and chronically damaged bowel mucosa contribute to malabsorption.[4] Occult blood loss also may occur, contributing to iron deficiency.

Micronutrient deficiencies in patients with IF can occur during the transition to full enteral nutrition (FEN) and may persist after successful transition.[5] Deficiencies of fat-soluble vitamins (A, D, E, and K) and certain minerals, such as zinc, are likely to develop because of uncertain absorption once PN is discontinued.[6] Micronutrient deficiencies can result in an increased risk of infections, anemia, growth failure, and, in extreme cases, death.[7-10] In the present study, we evaluated the prevalence of deficiencies of iron, zinc, magnesium, phosphorus, selenium, copper, folate, and vitamins A, D, E, and B12 during transition to enteral nutrition (EN) and after successful transition to FEN. We then examined risk factors for developing these deficiencies.

Methods

This single-center retrospective study involved a review of electronic medical records and databases of patients with IF seen at the Intestinal Care Center of Cincinnati Children's Hospital Medical Center between August 1, 2007, and July 31, 2012. A total of 256 patients were identified, of whom 178 met the inclusion

EN	Enteral nutrition
FEN	Full enteral nutrition
HAZ	Height-for-age *z*-score
IF	Intestinal failure
PN	Parenteral nutrition
WAZ	Weight-for-age *z*-score

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criteria, which included: (1) diagnosis of IF, defined by the need for PN support for longer than 30 days; (2) measurement of at least 1 micronutrient during or after transition to EN; and (3) follow-up in the Intestinal Care Center of Cincinnati Children's Hospital Medical Center during the study period. Patients with a history of liver, small bowel, combined, or multivisceral transplant were excluded.

Approval was obtained from the Institutional Review Board of the Cincinnati Children's Hospital Medical Center. Both caregiver consent and patient assent were waived because patients were deidentified and this study did not involve any direct patient contact, relying only on analysis of data obtained during routine patient care.

Electronic data for eligible patients were retrieved, including birth age, birth weight, sex, ethnicity, weight and height, gestational age, duration of PN, duration off PN, residual bowel length, resected part of small bowel, history of cholestasis, short gut syndrome, and multivisceral transplant. Serum levels of iron, total iron-binding capacity, ferritin, zinc, magnesium, phosphorus, selenium, copper, folate, and vitamins A, D, E, and, B12 during the transition from PN to EN and after successful transition to FEN were retrieved. Data were obtained longitudinally for each visit available throughout the follow-up period. Patient follow-up in the outpatient clinic depended on the severity of disease and clinical status. Patients who are weaned off PN are typically seen for follow-up visits every 6 months and evaluated for micronutrient deficiencies annually. Patients on PN are seen in clinic weekly during the initial posthospital period, with the frequency decreased to monthly when stable and up to every 6 months with long-distance referrals who are clinically stable. Micronutrient supplementations include multivitamins plus minerals for patients on total PN and oral/tube multivitamins for patients fully transitioned to FEN.

Transition to EN was defined as the period during which the patient received between 20% and 100% of estimated required nutrition enterally. FEN was defined as the patient's ability to tolerate 100% of the estimated required nutrition enterally for >2 weeks. This definition of >2 weeks has been used previously to define enteral independence.[5,11]

Low serum levels were used to define deficiencies. Serum 25-hydroxyvitamin D concentrations was measured by radioimmunoassay with I^{125}-labeled tracer (DiaSorin, Stillwater, Minnesota). Values <20 ng/mL and 20-30 ng/mL were defined as vitamin D deficiency and insufficiency, respectively. Abnormal total and direct bilirubin levels were >1.9 mg/dL and 0.3 mg/dL, respectively. Normal ranges for vitamins A, E, and B12 were 200-490 μg/L, 5.0-20.0 μg/mL, and 211-911 pg/mL, respectively. Serum folate ≥5.38 ng/mL was normal. Normal ranges for serum copper and iron were 80-155 μg/dL and 50-175 μg/dL, respectively. Iron deficiency was defined as serum iron <50 μg/dL or an transferrin saturation of <20% or serum ferritin of <30 ng/mL for males, and <15 ng/mL for postmenarchal females. The normal ranges for serum selenium, magnesium, and phosphorus were 23-190 μg/L, 1.5-2.3 mg/dL, and 2.9-4.6 mg/dL, respectively. Normal serum zinc level is 60-120 μg/dL. Iron deficiency anemia was suspected if the mean corpuscular hemoglobin was <79 fL, transferrin saturation was <20%, or serum ferritin was <30 ng/mL for males, and <15 ng/mL for postmenarchal females in the presence of age-defining anemia.

The percentage of expected residual bowel length was calculated using criteria described by Struijs et al[12] based on patient length. Bowel length percentages of 10% and 50% were used in this analysis, based on a previous definition of short bowel syndrome and outcome data.[13] The weight and height variables were converted to sex- and age-specific *z*-scores using the National Center for Health Statistics reference[14] and the World Health Organization standard.[15] Stunting and wasting were defined as *z*-scores <−2 SD below the age- and sex-specific reference means.[14,15]

The data were analyzed using SPSS version 19 (IBM, Armonk, New York). The χ^2 and Fisher exact tests were used to test significant association of the categorical variables. The distributions of all continuous variables were checked for normality using the Shapiro-Wilk test. The *t* test was used to compare the means of normally distributed continuous variables, and Mann-Whitney *U* test was used for non-normally distributed data. Univariate analyses examined the following independent variables and micronutrient deficiency during and after successful transition to FEN: age, ethnicity, sex, birth weight, health insurance, primary gastrointestinal diagnosis, history of short gut syndrome, presence of cholestasis, absence of ileocecal valve, ileal resection, residual bowel length, height-for-age *z*-score (HAZ), weight-for-age *z*-score (WAZ), duration of PN, duration off PN, route of feeding, formula, and micronutrient supplementation. Logistic regressions were used to adjust for all significant independent variables. A *P* value <.05 was considered significant, and all reported *P* values are 2-sided.

Results

Characteristics of the study subjects are presented in **Table I**. Among the 118 patients with height and weight data available at the beginning of the transition to EN, 53 (44.9%) had an HAZ <−2. Fifty-seven of 136 patients (41.9%) had an HAZ <−2 by the time of FEN. This difference in HAZ between the 2 periods was not significant (P = .27). Fifty-three of 120 patients (44.2%) had a WAZ <−2 at transition to EN, and 52 of 139 patients (37.4%) had a WAZ <−2 by the time of FEN. There was no significant difference in WAZ between the 2 periods (P = .63).

The prevalence of various micronutrient deficiencies during the transition to EN is shown in **Figure 1**. Sixty-four of 120 patients (53.3%) were receiving micronutrient supplementation during the transition from PN to EN, compared with 101 of 138 (73.2%) after successful transition to FEN (P < .001). More than one-half of the patients (56%) had at least 1 mineral deficiency, 35.4% had at least 1 vitamin deficiency, and 33.1% had multiple micronutrient deficiencies.