The nonspecific signs and symptoms of zinc deficiency and the current lack of a sensitive biomarker require that clinicians recognize the scenarios in which zinc deficiency may occur and obtain a targeted medical evaluation

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Update on Zinc Deficiency and Excess in Clinical Pediatric Practice by Nancy F. Krebs

Key insights

A large percentage of the global population is affected by mild to moderate zinc deficiency, particularly in low-income settings. Addressing this deficiency by means of zinc supplements is highly effective, with demonstrated benefits for pneumonia, diarrhea, and growth impairment. This article addresses the key clinical parameters for identifying zinc deficiency, assessing zinc status and applying the appropriate interventions.

Current knowledge

Zinc deficiencies can be categorized according to their etiological origins. Primary zinc deficiency occurs in older infants who have been mainly breastfed and weaned on traditional complementary foods. Genetically based zinc deficiencies, such as acrodermatitis enteropathica and transient neonatal zinc deficiency, arise as a consequence of mutations in zinc transporter proteins in the gut and mammary gland, respectively. Acquired zinc deficiency is associated with specific subgroups, such as premature infants and those with clinical conditions including celiac disease, cystic fibrosis, and liver disease.

Practical implications

Clinicians are advised to assess zinc status, particularly in patients at risk of acquired zinc deficiency. Dietary habits and the presence of potential gastrointestinal pathologies are among the major factors that can affect zinc status. Where applicable, zinc supplementation should be integrated within the clinical management strategy. In infants and young children, supple-

Imbalances in zinc homeostasis contribute to the risk of deficiency.

mentation via fortification of human milk, formula, or infant weaning foods is an effective means of ensuring adequate zinc intake.

Recommended reading

Krebs NF, Westcott JE, Culbertson DL, Sian L, Miller LV, Hambridge KM: Comparison of complementary feeding strategies to meet zinc requirements of older breastfed infants. *Am J Clin Nutr* 2012;96:30–35.

Update on Zinc Deficiency and Excess in Clinical Pediatric Practice

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Key Messages

- The nonspecific signs and symptoms of zinc deficiency and the current lack of a sensitive biomarker require that clinicians recognize the scenarios in which zinc deficiency may occur and obtain a targeted medical evaluation, especially a good diet history.
- Situations for which there is a high risk of acquired mild to moderate zinc deficiency include older breastfed infants and toddlers with low zinc intake, premature infants with high requirement and altered homeostasis, and gastrointestinal diseases or conditions in which absorption may be impaired and losses increased.
- The molecular basis of the two genetic zinc deficiency syndromes, acrodermatitis enteropathica and acquired zinc deficiency of lactogenic origin, is likely to be more complex than a single gene mutation and the clinical presentations are often more subtle than the classically described constellation of signs and symptoms.

Key Words

Zinc deficiency · Acrodermatitis enteropathica · Transient neonatal zinc deficiency · Premature infant · Breastfed infant · Assessment of zinc status · Zinc therapy

Abstract

The critical importance of adequate zinc status to human health, including normal growth and development, is indisputable. The high prevalence of zinc deficiency on a global

basis and its importance to public health have been well documented through large-scale randomized controlled zinc supplementation trials. Similar evidence in the clinical setting, however, is much less widely available due to the nonspecific features of zinc deficiency and to the lack of sensitive biomarkers to detect zinc deficiency, especially that of a mild degree of severity. The current understanding of zinc homeostasis indicates that the primary determinants of zinc absorption are the amount of zinc ingested and dietary phytate, the latter having a major effect on zinc bioavailability. In normal as well as in many pathologic conditions, the gastrointestinal tract is the major site of zinc losses resulting from secretion of endogenous zinc into the lumen and subsequent excretion in the feces. The amount excreted is dependent on host status, the amount reabsorbed, and sometimes the presence of pathophysiologic conditions, including diarrhea and steatorrhea. Assessment in the clinical setting dictates that the clinician obtain a careful medical and diet history, recognize clinical presentations in which zinc adequacy may be compromised, and link this risk with nonspecific but plausible manifestations of deficiency. Examples discussed in this article include primary zinc deficiency due to dietary inadequacy (older breastfed infants or toddlers without zinc-rich complementary foods); genetically based deficiency (acrodermatitis enteropathica, acquired zinc deficiency of lactogenic origin), and acquired secondary deficiency in low birth weight and prematurity, gastrointestinal and hepatic disease, and cystic fibrosis. Evidence for efficacy of zinc therapy with pharmacologic doses for two conditions, Wilson's disease and viral upper respiratory infections, is also discussed.

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Introduction

Large-scale randomized controlled trials of zinc supplementation conducted over the past two decades have demonstrated the widespread existence of zinc deficiency in populations, and the responsiveness of conditions of public health significance to supplementation. From trials involving numerous locations, populations, and study designs, general consensus holds that diarrhea, pneumonia, and growth impairment are conditions associated with positive responses to zinc supplements. This provides the compelling basis for the conclusion that mild to moderate zinc deficiency is relatively common in low-resource settings. The dilemma for clinicians, however, is how to bring this public health evidence to the clinic or the bedside of an individual patient.

This article addresses this quandary, applying the current understanding of the biologic function and homeostatic regulation of zinc to clinical practice and to common clinical presentations. Specifically, an approach to recognition of risk for zinc deficiency, assessment of zinc status, and therapeutic interventions will be considered. The emphasis for this discussion will be high-resource settings, but, while the underlying etiology and degree of risk may differ in other settings, the principles are similar.

Brief Background on Zinc Homeostasis

As covered elsewhere in this series, zinc homeostasis is primarily dependent on an interplay between intestinal zinc absorption and excretion of intestinal endogenous zinc, with involvement of the kidney and bone (and possibly integument) contributing less prominently under normal circumstances. Absorption of dietary zinc is best characterized as a saturable process and is primarily determined by two factors: the amount of zinc ingested and dietary phytate [1, 2]. The zinc status of the host does not seem to be a major determinant of absorption efficiency. More responsive to host status is the excretion of intestinal endogenous zinc, which is normally conserved in the setting of marginal zinc absorption and provides a means to excrete 'excessive' absorbed zinc. The role of perturbations in the processes of zinc homeostasis differs with particular clinical scenarios. The predominant effects are broadly categorized for typical clinical presentations in table 1.

Primary Zinc Deficiency: Breastfed Infants

In healthy infants in the US, the most likely scenario for pure dietary zinc deficiency is in the older breastfed infant, especially one who has been exclusively or predominantly breastfed and has transitioned according to traditional complementary feeding practices. The biological basis for this scenario is multifactorial but predictable based on a current understanding of zinc homeostasis, which is summarized in the following paragraphs.

The zinc content of human milk is well documented to start at quite high concentrations (>3 mg/l) and to immediately, sharply, and progressively decline over the early months postpartum to <1 mg/l by 6 months [3]. Importantly, although the un-

derlying biologic mechanisms are not yet characterized, this pattern is physiologic and independent of maternal dietary intake or status. More limited data from the literature also consistently note that the zinc intake of the exclusively breastfed infant also declines over the first 6 months of postnatal life, i.e. an increased volume of milk intake does not compensate for the sharp decline in milk zinc concentrations [4]. A comparison of zinc intake and its potential absorption to physiologic requirements predicts that by about 6 months of age, the breastfed infant becomes dependent on other sources of zinc to meet physiologic requirements [5]. In usual circumstances, this will be from complementary foods. Due to the human's limited ability to compensate for low zinc intake, it is now clear that the quality of the complementary foods is critical to meet the zinc requirements of the older infant.

Recently published zinc absorption data for 9-month-old breastfed infants who were randomized to different complementary food regimens, including meat, a multiple-micronutrient fortified infant cereal, or an iron (only) fortified cereal, illustrate several concepts [6]. First, the absorption efficiency (fractional absorption) of zinc from human milk was relatively high compared to fractional absorption from complementary foods, but the actual amount of absorbed zinc was still lower. Thus, the recognized favorable bioavailability of zinc from human milk is likely driven mainly by its low zinc concentration and this bioavailability only partially compensates for the low intake [5]. Similarly, the lower intake of zinc in the unfortified cereal group was accompanied by a significantly

A comparison of zinc intake and its potential absorption to physiologic requirements predicts that by about 6 months of age, the breastfed infant becomes dependent on other sources of zinc to meet physiologic requirements.

Table 1. Disturbances of zinc homeostasis that contribute to risk of deficiency in different clinical conditions

Disease/condition	Mechanisms of putative zinc deficiency				
	reduced stores	low dietary intake	impaired absorption	increased intestinal endogenous losses	increased renal endogenous losses
Older breastfed-only infant		x			
Toddlers on mixed diets		x			
Premature/SGA infant	x	(x)*	x	x	x
Celiac disease			x	x	
Short gut syndrome			x	x	
Cystic fibrosis		(x)	x	x	
Liver disease		x	x		x

* Risk of inadequate intake if not receiving fortified human milk or preterm infant formula.

higher fractional absorption from complementary foods, but this was also insufficient to adequately compensate to meet requirements. Second, the zinc intake and absorption from the fortified cereal was not different from that of the meat group, confirming that zinc fortification of a relatively low-phytate food offers an efficacious means of meeting zinc requirements of older infants. Third, although the small sample sizes for each group preclude conclusions about the functional impact of the low zinc intake of the unfortified cereal group, this dietary pattern (ad libitum human milk, fruits and vegetables, and unfortified cereal) resulted in daily absorbed zinc less than two thirds the estimated physiologic requirement and an exchangeable zinc pool (EZP) size significantly lower than that of the other two groups [6].

Reliance on unfortified dietary staples with low zinc content and high phytate content complementary feeding is a perfect combination to develop at least mild zinc deficiency.

These data suggest that continuation of this pattern would eventually result in some functional deficit due to zinc deficiency, such as anorexia, growth faltering, and immune impairment, all features of mild zinc deficiency [7]. This represents not only a common dietary pattern for breastfed infants in the US, where meat is consumed by the minority of infants <12 months of age [8], but also represents the norm in many of the low-resource settings

where zinc deficiency has been observed [9]. Reliance on unfortified dietary staples with low zinc content and high phytate content complementary feeding is a perfect combination to develop at least mild zinc deficiency. The risk of deficiency is likely to be further exacerbated by recurrent bouts of acute diarrhea which result in increased endogenous losses.

The case vignettes 1, 2, and 3 (table 2) are typical of the clinical presentation of mild zinc deficiency in normal breastfed infants in our pediatric nutrition referral clinic. Reasons for the referral are slow growth and/or poor feeding. Diet history typically includes, in addition to breastfeeding, reliance on complementary foods that are low in zinc: fruits, vegetables, juice and water, unfortified pasta, and dairy products. As noted in the vignettes, iron deficiency is also common. On the premise that plasma zinc concentration is often normal in mild zinc deficiency [7], this biomarker is not routinely obtained. Rather, a 1- to 2-month empiric course of zinc supplementation (1 mg zinc/kg/day) is recommended, along with concurrent treatment of iron deficiency. The effectiveness of this approach is difficult to quantify, and it is not the only intervention, but the most common result in such 'classical' presentations is an improvement in growth and food intake.

The prevalence of zinc deficiency in this population is unknown. In small studies of 9-month-old breastfed infants in Denver, we have reported low plasma zinc concentrations in approximately one third of infants [10], using the cutoff of 65 µg/dl recommended for this age [11], suggesting that hypozincemia is not uncommon. This is supported by a similar rate (27%) reported in a large sample of 12- to 36-month-olds served by the Spe-

Table 2. Brief case vignettes (all compiled from the author's current pediatric clinical nutrition practice)

Patient	Chief complaint	Description
1 Healthy 15-month-old	Poor growth, no weight gain for 5 months	Breastfeeding 3 times/day; CF since 6 months, 'normal progression'; diet: yogurt, eggs, cheese, some meat/spaghetti, chicken (i.e. not avoiding meat); drinks: 600–720 ml water/day, no juice. PMHx: term infant; negative except URIs. Anthropometry: length/age 4%; weight/age 0.01%; OFC/age 13%; 82% of ideal body weight (i.e. mild to moderately wasted). Exam unremarkable. Labs: normal chemistries except iron deficient [ferritin 11 µg/l (low); MCV 76 (low normal); RDW 15.6 (high); vitamin D 19 ng/ml (low)]; CD screen negative
2 Vegetarian 19-month-old	Slow growth	Breastfeeding multiple times throughout day and night; CF at 4–5 months; not interested in food; grazes throughout day; sips of soy milk; vegan choices, including salty snacks for toddlers, pasta. PMHx negative. Anthropometry: length/age 6.4%; weight/age 0.60%; OFC/age 32%; 87% of ideal body weight. Exam unremarkable. Labs: normal complete blood count and chemical panel; ferritin 6 µg/l (low); % transferrin saturation 17 (low)
3 Healthy 11-month-old	Slow growth, poor appetite	Diet: breastfeeding 5–6 times/day; formula 6–7 oz/day; rice, fruits, lentils, cereal; refuses meats. PMHx: birth weight 2.5 kg; healthy. Anthropometry: length/age 1.9%; weight/age 0%; OFC/age 9%; 77% of ideal body weight (moderate wasting). Exam unremarkable, except thin. Labs: hemoglobin 10.6 g/dl; MCV 73 (low normal); RDW 15.3; ferritin 11.5 µg/l (low); % transferrin saturation 15 (low); vitamin D 16 ng/ml (low)
4 4-month-old, ex-32-week premature infant	Persistent, severe rash	Diet: exclusive breastfeeding. Labs: plasma zinc 6 µg/dl (normal range 60–110 µg/dl); breast milk zinc ~25% of normal for postpartum stage
5 11-month-old, ex-28-week premature infant	Lethargy and acute respiratory decompensation with viral illness	Diet: exclusive breastfeeding, no complementary foods; no multivitamins. PMHx: premature, adequate for gestational age, relatively benign NICU course; no immunizations. Anthropometry: <2nd percentile all parameters, corrected for prematurity. Exam: intubated; no rash, thin. Labs: hemoglobin 3.1 g/dl; MCV 60; RDW 36; albumin 3.2 g/dl; ferritin 7.2 µg/l (low); % saturation 4 (low); zinc 38 µg/dl (low); vitamin D 7 ng/ml (low)

CF = Complementary foods; PMHx = past medical history; URIs = upper respiratory infections; OFC = occipital frontal circumference; MCV = mean cell volume; RDW = red blood cell distribution width; CD = celiac disease.

cial Supplemental Nutrition Program for Women, Infants, and Children (WIC) in the US. In that study, consumption of sweetened beverages was negatively associated with serum zinc, and consumption of at least 15 g/day meat was positively associated with serum zinc level [12]. Since zinc deficiency often occurs without hypozincemia, these limited data suggest that mild zinc deficiency may be relatively common in infants and toddlers with these dietary patterns.

Genetically Based Zinc Deficiency

Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) is the prototype of the severest forms of human zinc deficiency. Before the beneficial effects of zinc therapy were recognized, this was a severe, progressive, and often fatal disease. It is a rare

autosomal recessively inherited disorder, now recognized to result from a partial block in intestinal zinc absorption due to mutations in the SLC39A4 gene, also known as the ZIP4 gene. The gene codes for hZip4, a transmembrane, histidine-rich protein, a member of the ZIP family of metal ion transporters which function in zinc uptake [13]. The classic phenotypic expression of this disease, the triad of a periacral and periorificial dermatitis, alopecia and diarrhea, is attributable entirely to a severe zinc deficiency state. The cutaneous lesions are initially eczematous, and then quickly progress to an erosive, psoriasiform or vesiculopustulous lesion, typically in the classic distribution. Although total body zinc is not greatly reduced in AE, plasma zinc concentrations are typically extremely low (e.g. <30 µg/dl). With improved characterization of the genetic mutations, however, the 'pathognomonic triad' is reported to be observed in a minority of AE cases

[14]. New mutations have also been reported, and it is suggested that a genotype-phenotype correlation is not as easily defined as previously assumed, suggesting that the molecular basis of the disease is complex [15]. Overall, mutations of SLC39A4 are observed in only about half of the index AE cases tested, with ~40% of the patients found to be homozygotes or compound heterozygotes, and 8% found to be heterozygotes [16].

In the clinical setting, the diagnosis of AE can be challenging because, currently, testing for the genetic mutation is not readily available. Historically, a key element in the diagnosis of AE was the rapid improvement of signs and symptoms of deficiency after oral zinc supplementation, with resolution within days to weeks. The differential diagnosis, however, also includes biotinidase deficiency, severe atopic dermatitis, or zinc deficiency from a defect in mammary gland secretion (described below), which can also present with signs of severe zinc deficiency and at a similar age as classic AE. Interruption of zinc therapy may help to distinguish between inherited AE and acquired zinc deficiency; symptoms will promptly recur with AE. The importance of a correct diagnosis is obvious, as true AE requires life-long high-dose zinc supplementation. Supporting the likelihood of more than a single mutation, in clinical practice we have had young patients who do not have classic findings of AE, but who appear to have zinc 'dependence' on the basis of persistent mild hypozincemia (~50 µg/dl) responsive to supplementation; parental reports of anorexia and mild, nonspecific dermatitis; and improved growth with supplementation.

Acquired Zinc Deficiency of Lactogenic Origin (Transient Neonatal Zinc Deficiency)

The clinical literature contains numerous reports of severe zinc deficiency in breastfed infants attributable to an inability of the mother's mammary gland to secrete normal quantities of zinc [17, 18]; reports are especially common for infants having been delivered prematurely [19, 20]. The low zinc levels in milk occur despite an otherwise apparently normal maternal zinc status. The specific mutation or mutations of zinc transporters localized to the mammary gland, e.g. SLC30A2 (ZnT-2), responsible for this condition in humans is an area of active research [21–23]. This mutation is characterized by markedly low milk zinc concentrations (~25% of normal for

stage of lactation), resulting in severe zinc deficiency in the exclusively breastfed infant. Supplemental zinc to the infant easily treats the infant's deficiency, as there is no absorptive defect in the infant.

The prevalence of this defect is unknown, but clinical impression is that it is not rare. For example, in a large cohort of Chinese women, two polymorphisms of the SLC30A2 gene explained 3.23% of total variance in milk zinc concentrations [24]. Contrary to early observations, which suggested that the primary phenotypic presentation of this defect in mammary gland zinc secretion zinc deficiency was in premature infants due to their special vulnerability to zinc deficiency (see below), it is now clear that term infants are also susceptible [17, 18].

Case 4 (table 2) illustrates the vulnerability of premature infants for severe zinc deficiency due to low milk zinc concentrations. This infant had not received fortified human milk during her hospital course and presented with a classic dermatitis and profoundly low plasma zinc concentration by 3–4 months postnatal age. She responded well to supplementation and recovered completely. For her mother's subsequent pregnancy and lactation cycle, low zinc in breast milk was again confirmed, and the infant was prophylactically supplemented with zinc with good outcome.

Acquired Zinc Deficiency

Premature Infants

Zinc deficiency has been well documented in hospitalized premature and low-birth-weight infants if supplemental zinc was not provided. Signs of deficiency include growth impairment (linear and ponderal), characteristic dermatitis similar to that described above for AE, and moderately low plasma/serum zinc concentrations [20, 25–27]. In one large series from a hospital population, the strongest clinical risk factors include low gestational age, small for gestational age (SGA), and intestinal resection [28].

The challenges of investigating postnatal zinc homeostasis in this population are considerable, due to the often tenuous and fluctuating clinical state. The etiology of deficiency in this population thus represents a combination of factors: low body 'stores' or tissue levels due to the missed opportunity for zinc accretion during the last trimester of pregnancy; increased endogenous losses from

***Supplemental zinc to the infant
easily treats the infant's deficiency, as
there is no absorptive defect in the
infant.***

the kidney and from the gastrointestinal tract, and a potentially marginal intake. Each of these aspects will be briefly discussed in the following sections.

More than two decades ago, Zlotkin and Cherian [29] reported higher concentrations of hepatic zinc-binding metallothionein in premature compared to term infants. The smaller liver size in the premature infants, however, resulted in less available zinc for post-natal utilization. To estimate the size of the EZP at birth in premature infants, we administered zinc stable isotope intravenously within the first 24 h after delivery, before significant nutrition support had been initiated [30]. The results supported a relatively larger EZP size on a body weight basis, at >10 mg/kg compared to ~5 mg/kg observed in term breastfed infants at 2–5 months post-natal age [31], but a lower absolute EZP size. SGA infants had a significantly smaller EZP size compared to appropriate-for-gestational-age infants of similar degrees of prematurity [30]. If these results are reproduced, they suggest a particular vulnerability for SGA premature infants to zinc deficiency [32].

Preterm infants' dietary zinc intake in most neonatal intensive care units (NICUs) in the US is provided either through fortified human milk, fortified formulas designed for premature infants, and/or parenteral nutrition support. Standard fortification levels result in high zinc intakes relative to body weight: 2.7 mg/kg/day, which is more than 4-fold greater than exclusively breastfed term infants at 2 weeks of age [4, 33]. As the promotion of human milk in NICUs, either mothers' own or donor milk, has gained momentum, there is potential for more variable and possibly marginal zinc intake if fortification is not assured [34]. To date, limited data suggest that zinc concentrations in preterm milk may be higher than those of term milk, although this has not been consistently observed. Furthermore, the pattern of declining zinc concentrations in the early postpartum months does not differ between preterm and term human milk [35, 36]. Thus, as a premature infant approaches 40 weeks post-conceptional age, the decline in milk zinc concentrations will already have been substantial and may well be progressively suboptimal to sustain normal growth. Additionally, donor milk is often provided by mothers at least several months postpartum [34], which is likely to be

lower in zinc concentration compared to mothers' own milk. Fortified human milk should provide adequate zinc intake. When infants are discharged home, however, fortification is much less common and zinc supplementation is not routinely recommended nor easily practiced due to lack of commercial liquid zinc supplements.

Complete zinc homeostatic data are limited for pre-term infants, and methods reported in the literature have ranged from traditional balance to complete stable

isotope metabolic studies, or a combination of methods. Fractional zinc absorption by the premature infant has been reported to be of a similar magnitude to that of older infants, but absorptive capacity appears to be lower, perhaps due to shorter intestinal length [37, 38] and/or immaturity of zinc trans-

porters [38]. Several reports indicate high renal losses of zinc in young premature infants [33, 39, 40]. Diuretics commonly used in this population are likely to further increase zinc losses. Few data are available for endogenous fecal losses as a potential factor impacting zinc requirements. Our own data indicated relatively high losses, but these must be considered in light of the very high zinc intake [33]. Some inefficiency of reabsorption of intestinal endogenous zinc appeared likely, possibly related to shorter intestinal length, to concurrent fat malabsorption, or to a combination of these or other factors.

To summarize, the available data confirm a strong susceptibility of premature infants to zinc deficiency if intakes are not bolstered, either through fortification of human milk or formula, or by use of supplements. Because of the vulnerability and complexity of this patient group, zinc deficiency should remain a consideration for any preterm infant who is not growing well in the face of apparently adequate energy and macronutrient intake; has not consistently received a zinc-fortified human milk or formula designed for preterm infants; has sustained any gastrointestinal resection or insult, or is on diuretic therapy. For the preterm infant who is predominantly breastfed after discharge, zinc supplementation should be undertaken if good growth is not sustained. Case 5 (table 2) represents an extreme illustration of several aspects of the risk of zinc deficiency (and other micronutrient deficiencies) after hospital discharge.

The available data confirm a strong susceptibility of premature infants to zinc deficiency if intakes are not bolstered, either through fortification of human milk or formula, or by use of supplements.

Table 3. Clinical conditions associated with increased risk of zinc deficiency

Clinical condition	Presentation	Treatment
Celiac disease	Erosion of the mucosa of the proximal small intestine, anorexia, diarrhea, short stature	Institution of a gluten-free diet, with or without zinc supplementation
Cystic fibrosis	Exocrine pancreatic insufficiency and intestinal mucosal abnormalities, hypozincemia, growth faltering, diarrhea, dermatitis similar to AE	Multi-vitamin-mineral preparations containing zinc designed specifically for patients with CF; for infants and children <2 years of age, consider 6-month supplementation trial if growth faltering persists
Liver disease	Dermatitis, altered mental status, impaired night vision, hypogonadism, impaired immune function, depressed wound healing	Consider high-dose zinc supplementation if signs of deficiency are evident

Clinical Conditions Associated with Increased Risk of Zinc Deficiency

The paramount importance of the gastrointestinal tract for zinc homeostasis is consistent with the observed benefits of zinc supplementation in the setting of acute diarrhea. Virtually all supplementation trials have been conducted in low-resource settings, however, and whether the efficacy that has been observed in most [41], but not all [42], trials is due to correction of underlying zinc deficiency or to local or pharmacologic effects remains uncertain. In clinical practice, an empiric 7- to 10-day course of zinc supplementation per World Health Organization recommendations is reasonable for a young child with diarrhea, especially if recovery has been slow and/or premorbid dietary intake was marginal. There are no formal guidelines or recommendations for routine zinc supplementation in children in developed countries. Select pediatric patient groups with gastrointestinal pathology, such as those with short gut syndrome, intestinal failure, or other causes of malabsorption and/or increased endogenous intestinal losses, are at risk for hypozincemia [43] and should be considered for zinc supplementation (table 3).

Celiac Disease

This relatively common condition is an immune-mediated systemic disorder elicited by dietary gluten in genetically susceptible individuals and is characterized by variable degrees of erosion of the mucosa of the proximal small intestine. The presentation of infants and young children with celiac disease (CD) overlaps with several of the features of zinc deficiency: anorexia, diarrhea, and short stature. Not surprisingly, zinc deficiency (on the ba-

sis of hypozincemia) has been reported in children and adults with CD [44]. Studies applying stable isotope methods to patients with CD have reported both impaired zinc absorption [45] and increased fecal losses of endogenous zinc [46]. Institution of a gluten-free diet has been reported to result in normalization of plasma zinc levels, with or without zinc supplementation [44, 47]. Given the variable clinical presentation of CD, however, along with the difficulty of assessing zinc status, it is reasonable to institute an empiric trial of zinc supplementation at the time of diagnosis for individuals with symptomatology consistent with deficiency or with persistent signs or symptoms suggestive of zinc deficiency despite initiation of a gluten-free diet.

Cystic Fibrosis

The gastrointestinal manifestations of this common heritable condition include exocrine pancreatic insufficiency and intestinal mucosal abnormalities. Hypozincemia has been documented in young infants identified by newborn screening prior to initiation of pancreatic enzyme therapy [48]. In settings without newborn screening, presentation is typically later in infancy, with associated growth faltering, diarrhea, and a dermatitis similar to AE [49]. Growth faltering observed in older children with cystic fibrosis (CF) is undoubtedly multifactorial, including malnutrition, but in one report, older children's total zinc intake and zinc status were adequate and unrelated to growth status [50]. In contrast, in another retrospective chart review, high-dose (5 mg zinc/kg/day) supplementation was associated with beneficial effects on growth and pulmonary function [51]. However, no con-

trolled trials are available that replicate these effects. One controlled small trial in children demonstrated a reduction in days of pulmonary infection and antibiotic use over a year's time with a relatively high daily dose of zinc (30 mg); effectiveness was greater in those with low plasma zinc levels at the outset [52].

There is a strong plausibility for zinc deficiency in infants and children with CF. Stable isotope studies have demonstrated lower absorption in infants and adolescents, especially without enzyme replacement therapy [53], and fecal excretion of endogenous zinc was observed in infants to significantly correlate with fecal fat excretion [54]. For infants and children <2 years of age who are not growing despite apparently adequate nutritional intake, a 6-month trial of zinc supplementation (1 mg zinc/kg/day) has been recommended [55]. Multi-vitamin-mineral preparations designed specifically for patients with CF now routinely contain zinc. The potential benefits of higher-dose supplementation have not yet been rigorously tested.

Liver Disease

A comprehensive review of perturbed zinc metabolism in several types of liver diseases in adults documents its multidimensional aspects [56]. The etiology of zinc deficiency is likely to be multifactorial, including reduced dietary intake, increased urinary excretion, altered intestinal transport, and induction of hepatic metallothionein resulting in zinc sequestration. The manifestations of zinc deficiency reported in liver disease are likewise numerous, including dermatitis, altered mental status, impaired night vision (related in part to vitamin A deficiency), hypogonadism, impaired immune function, and depressed wound healing. Hypozincemia and substantially increased urine zinc losses were documented in children with liver failure prior to transplant. Transplantation was associated with normalization of urine zinc losses and zinc status, without supplementation [57]. Well-controlled trials of zinc supplementation have not been conducted in either adults or children, but biologic plausibility is strong for a potential benefit, and further investigations appear indicated. If such supplementation is to be undertaken, a pharmacologic dose is likely warranted; adult studies have often used 50 mg zinc/day, taken with a meal [56].

Zinc Supplements as Therapy in Children

In pediatric practice, especially in settings where nutritional status is presumed to generally be adequate, use of pharmacologic zinc treatment is relatively uncommon. Two examples are discussed below.

Wilson's Disease

The basis of zinc supplementation as a monotherapy for Wilson's disease (WD) is that it inhibits intestinal copper absorption and stimulates synthesis of hepatic metallothionein, which binds copper with higher affinity than zinc. Use of zinc was approved by the US Food and Drug Administration in 1997. Doses in the range of 50–75 mg elemental zinc per day have been used in children. Two reports, including one with a 10-year follow-up on 22 children, support efficacy of zinc therapy for young presymptomatic children. Findings in both reports included improvement in hepatic inflammation, substantially reduced hepatic transaminases and urine copper excretion, and (in the larger series) hepatic copper content. Neither series reported evidence of zinc toxicity, and growth was normal [58, 59]. A systematic review, which included pediatric reports, concluded that zinc therapy was preferred over D-penicillamine for treatment of presymptomatic and neurological patients, whereas D-penicillamine was preferred for patients presenting with hepatic signs [60]. Tolerance to zinc therapy was also better than for D-penicillamine. Multicenter prospective randomized controlled comparative trials are clearly warranted to extend the current understanding of the utility and limitations of zinc therapy for WD in the pediatric population.

Blinded randomized controlled trials showed a shortened duration of symptoms with zinc if therapy was initiated shortly after the onset of symptoms.

Zinc and the Common Cold

Zinc has been investigated extensively in developed countries for its ability to treat 'the common cold', or upper respiratory infections (URI). This is an intervention that has had modest 'uptake' in pediatric practice in developed countries, but it provides an example of a pharmacologic effect, since most individuals would be presumed to have sufficient zinc status at baseline. The theoretical basis for zinc's effectiveness against viral-induced URIs includes inhibition of viral replication or of intracellular adhesion, or an enhanced innate immune response at the mucosal surface [61, 62]. Zinc lozenges and intranasal sprays have both been evaluated to shorten the length of the URI symptoms. Results among trials have been quite mixed, with approximately half of the blinded random-

ized controlled trials showing a shortened duration of symptoms with zinc if therapy was initiated shortly after the onset of symptoms and if contact was directly to the oropharynx [62, 63]. Although supplementation for at least 5 months was associated with a significantly reduced incidence of URI, school absenteeism and prescription of antibiotics in children, these findings have been questioned due to the small sample size and lack of replication. Many have noted the potential for zinc lozenges to produce side effects, including bad taste and nausea. All reviews to date have concluded that, despite likelihood of efficacy, data are insufficient to make recommendations regarding dose, formulation and duration [64, 65].

Otitis Media

Data are more limited for use of zinc therapy for the prevention of otitis media, and systematic reviews do not yet support a role for zinc supplements to reduce the occurrence of otitis media in healthy children [66].

Excessive Exposure to Zinc

Zinc is generally considered to be relatively nontoxic. Excessive zinc can cause copper toxicity, but under most clinical situations, this is not of practical importance. For example, supplementation of 10 mg/day for 4 months in infants was not associated with hypocupremia [67]. More recently, a 4-month trial in adolescent boys found no evidence of adverse effects on an extensive array of indicators of copper status from either 5 or 10 mg of daily supplemental zinc in addition to dietary zinc intakes which were at or exceeded the tolerable upper intake levels [68, 69]. Several case reports of symptomatic copper deficiency have been reported in adults with inappropriately excessive intake of dental fixative [70]. Excessive zinc has been proposed to be a factor in autism [71], but no controlled trials have demonstrated a relationship.

Assessment of Zinc Status

The paucity of sensitive biomarkers of zinc status is well documented [72]. The use of plasma or serum zinc remains the best, albeit imperfect, biomarker of zinc status. It is most useful for characterizing the zinc status of a population [73]. The major biological limitations of

Assessment of the risk of zinc deficiency in the clinical setting thus relies on a good history, including especially diet and feeding history, and a review of systems addressing potential gastrointestinal pathology.

plasma zinc include its low sensitivity to indicate marginal zinc status; its responsiveness as a negative acute-phase reactant to acute and chronic inflammation, and its fluctuation in response to meals and time of day. Zinc contamination of samples from skin at the time of phlebotomy or

from zinc in the collection materials is also a potential confounder [74].

Assessment of the risk of zinc deficiency in the clinical setting thus relies on a good history, including especially diet and feeding history, and a review of systems addressing potential gastrointestinal pathology. Anthropometry, though nonspecific, can provide evidence of growth faltering, and exam is revealing if dermatitis is present. Perhaps most important is the recognition of high-risk scenarios for zinc deficiency, such as those described above and as summarized in table 1. The overarching components of zinc homeostasis include dietary intake and bioavailability, either of which can limit daily absorbed zinc, and endogenous losses, which can be increased by intestinal, renal, or systemic pathology. The nonspecific signs and symptoms of zinc deficiency, especially mild, dictate the need for a high index of suspicion; there is simply no alternative.

Response to supplementation is considered evidence of a preexisting deficiency, but in clinical practice, it is rare that zinc supplementation is the only intervention initiated. Nevertheless, the myriad critical functions of zinc and the clear adverse effects of deficiency, plus the low toxicity of moderate supplementation warrants an empiric supplementation trial if a comprehensive assessment suggests risk of deficiency. Although not universally apparent, the potentially very rapid improvement and resolution of features of zinc deficiency is particularly gratifying and, in some modest way, compensates for the challenges posed to the clinician by this critical but cryptic micronutrient.

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