Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Specific Care Question: Use of Supplemental Zinc in Children

Team Members:
Brandon Newell, MD; Margo Humenczuk, MA, RD, MBA; Barbara Warady, MS, RD and Facilitator Nancy Allen, MS, RD
Librarians: Benjy Stein MSLIS MSED. & Keri Swaggart, MLIS, Evidence Based Scholars: Kate Collum, RN, Sally Shubat MA, CCC-SPL, Nancy Allen, MS, MLS, RD, Jarrod Dusin, MS, RD, LD, CNSC, Daniela Pirvu, RN, Christina Gutierrez, RN

Inclusions criteria: The question specifically synthesized literature on zinc and absorption (of zinc), growth, failure to thrive, eczema, epidermolysis Bullosa (EB) and warts. Background information on assessing zinc status, harms of zinc supplementation, and contamination of zinc supplements were synthesized.

Exclusions criteria: This Question does not address zinc supplementation in children with ileostomies, burns or who participate in sports. Poor appetite is a basic and non-specific feature of zinc deficiency (National Academy of Science, 2001, p. 447) and is not included in this review ie studies were not identified.

Recommendations:
1. Based on moderate quality evidence, a strong recommendation is made not to obtain a serum zinc level to determine zinc deficiency in individuals. (Synopsis- Figure 1, National Academy of Science (2001) pp 452 & DeBenoist 2007)

2. Based on high quality evidence a strong recommendation is made to treat zinc salts as equivalents. (Figure 9, Figure 10, Figure 11 and Figure 12

3. The consideration of zinc supplementation is recommended for the following groups:
   a. Based on strong evidence, strict vegetarians (major food staples are grains and legume AND dietary phytate:zinc molar ratio >15:1). National Academy of Science (2001) p. 480
   b. Based on moderate evidence former preterm or small for gestational age infants (Figure 2)

4. Based on high quality evidence of upper limits to absorption rate a dose no greater than 15 mg elemental zinc/day is recommended. (Tran, 2004)

5. Based on practical issues with dosing (only forms available on CMH formulary are 15 mg & 50 mg tablets and 50 mg capsule) try to use an age appropriate multivitamin/multi-mineral supplement zinc. Based on the

<table>
<thead>
<tr>
<th></th>
<th>Infant 0-6 mo</th>
<th>7-12 mo</th>
<th>1-3 yrs</th>
<th>4-8 yrs</th>
<th>9-13 yrs</th>
<th>14-18 years</th>
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<td></td>
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<tr>
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<td>Girls</td>
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<tr>
<td>Dietary Reference Intake (DRI) (mg/d)</td>
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<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
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<tr>
<td>Tolerable Upper Limit (mg/d)</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>23</td>
<td>34</td>
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</table>

Table 1
*Tolerable Upper Limit is defined as the highest level of daily nutrient intake, from all sources, that is likely to pose no risk of adverse health effects for almost all individuals.

QA/QI on this topic will be a run chart of serum zinc levels drawn. I will request a quarterly report, by ordering service/ambulatory location.

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**Significance and importance of the question:** Zinc is a known co-factor for the enzymes DNA and RNA polymerase. Deficiency, although not common, impairs growth. There is no good biological marker of an individual's zinc status. "Plasma and serum zinc concentrations do not seem to be sufficiently sensitive to serve as a subsidiary indicator" (National Academy of Science, 2001, page 452). However, serum zinc appears to be an indicator used by most, but it is influenced by the time of day, postprandial state and presence of stress (National Academy of Science, 2001). The Nutrition Department at Children's Mercy Hospital and Clinic in Kansas City (CMH&C) recommend supplemental zinc for children who have low serum zinc levels (<70 mcg/dl).

The recommendation for treatment (Lexicomp™, 2011) that is age based:

- **0-6 months** – 3 mg/d
- **7-12 months** 5 mg/d
- **1-10 years** – 10 mg/d
- **>10 years** 15 mg/d

**Treatment of Zinc deficiency: Oral:**

- Infants and Children: 0.5-1 mg elemental zinc/kg/day divided 1-3 times/day; somewhat larger quantities may be needed if there is impaired intestinal absorption or an excessive loss of zinc
- Adults: 110-220 mg zinc sulfate (25-50 mg elemental zinc)/dose 3 times/day

The Pharmacy at CMH&C stopped compounding zinc suspensions in July, 2008. Our pharmacy has two zinc supplements on formulary (a) 15mg elemental zinc (as gluconate) tablet and (b) and 50 mg elemental zinc (as sulfate) capsule. For inpatient use, a tablet/capsule is dispensed with instructions to make a slurry for administration for children who do not swallow. For children who are able to take a tablet/capsule instruction to split a tablet/capsule is provided for doses less than provide in the pill or capsule.

Here is an example, retrieved from PHRED for a child who was prescribed to take 15 mg of elemental zinc

**Order Comments**

"At home, patient was taking medication with the following details: Comments: Crush and or daily 1 tbl (abbreviation means tablet) and mix with 3 ml of water, five pt 1 ml of mixture" signed by APN

**Product note**

"Zinc Sulfate 220 mg is equivalent to 50 mg of Elemental Zinc. If GI upset occurs, take with food. If Necessary, Open capsule and dilute 50 mg of elemental zinc sulfate with 3 mLs sterile water. Give 1 ml to equal 16.7 mg. Product has 30 minute stability." signed by RPh.

At discharge families have to be able to

- Read supplement labels and discern between elemental zinc and zinc salt on the label.
- For children who do not swallow, crushed tablet or capsule to be administered the correct fraction
- For children who do swallow, cut or separate the zinc tablet/capsule and administer the correct fraction

However, see the attached summary of the IOM report that establishes the requirements of zinc as a nutrient. Zinc is a dietary supplement and not a drug. It is not dispensed by most outpatient pharmacies, although it is sold in "drugstores" grocery stores and health food stores. It is not a covered by insurance: either private, Medicare or Medicaid. Families have to choose the appropriate product from the dietary supplement aisle. Zinc is poorly water soluble and readily precipitates out of the slurry created in this fashion.

The Nutrition Department desired to update the handout that was created to assist prescribers and families to be consistent with current dosing.
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To do so, the following questions arose:

- Which zinc salt is best absorbed?
- What is the best test to show zinc deficiency?
- Does supplemental zinc improve growth in:
  - Failure to thrive (FTT)
  - Epidermolysis Bullosa
  - Eczema
  - Warts

The goal of this Specific Clinical Care question is to understand how supplemental zinc is prescribed at our hospital, and to evaluate evidence that supports the zinc supplementation. For the first goal, data was pulled from the EMR at CMH&C (PHRED) for the Jan 2010 to Jan 2011. MRN, Zinc Order (only Inpatient) and Result of laboratory test for serum zinc (Inpatient and Ambulatory) was obtained.

Orders:
A summary of orders for supplemental zinc (timeframe Jan2010- Jan 2011)
- 101 unique MRNs were identified
- 176 orders were written for supplemental zinc
- 75 orders were duplicates on the same patients changing form of zinc supplement (i.e. from suspension to tablet, from 15 mg tablet to 50 mg tablet/capsule)
- The range of ordered zinc doses were 2 mg/d to 150 mg/d.

The Graph 1 is a representation of the number of CMH in-patients who had physician orders to receive zinc supplements by inpatient team.
The Chart 1 is a representation of the various doses ordered for the patients who had zinc supplements ordered.
See Graph “Range of Zinc Doses”.

Laboratory
A summary of orders for serum zinc levels (timeframe Jan 2010-Jan 2011)
Graph 2

See Graph "Range of Serum Zinc Level (mcg/dl)"

- 59 unique MRNs had at least one serum zinc level ordered during the inpatient or observation stay.
- The range of serum zinc was from 30 mcg/dl to 121 mcg/dl. (Median s. zinc was 60 mcg/dl).
- 25% of the labs were drawn after 0600.

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<tr>
<th>Dose (mg)</th>
<th>Count</th>
<th>Dose (mg)</th>
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<td>12</td>
<td>12.5</td>
<td>1</td>
<td>150</td>
<td>1</td>
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</table>
Peach highlight denotes the amount of elemental zinc in either the zinc tablet or capsule on CMH formulary. Doses not in peach are manipulated by Nursing to achieve the ordered dose.

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<th>Origin of Order</th>
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<tr>
<td>4 Sutherland Tower</td>
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<td>5 Henson Tower</td>
<td>1</td>
</tr>
<tr>
<td>5 Sutherland Tower</td>
<td>5</td>
</tr>
<tr>
<td>5 West Observation</td>
<td>1</td>
</tr>
<tr>
<td>6 Henson Tower</td>
<td>2</td>
</tr>
<tr>
<td><strong>Outpatient</strong></td>
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</tr>
<tr>
<td>Allergy Clinic</td>
<td>3</td>
</tr>
<tr>
<td>SC Allergy Clinic</td>
<td>6</td>
</tr>
<tr>
<td><strong>Altered Nutrition Clinics</strong></td>
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<tr>
<td>BC Ready Set Grow</td>
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<tr>
<td>SC Eating Disorders Clinic</td>
<td>10</td>
</tr>
<tr>
<td><strong>Dermatology Clinic</strong></td>
<td></td>
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<tr>
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<tr>
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<td>Sickle Cell Clinic</td>
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<td><strong>Other Clinics</strong></td>
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<table>
<thead>
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<tr>
<td>Down Syndrome Clinic</td>
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<td>Rehabilitation Clinic</td>
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<tr>
<td>SC Ophthalmology Clinic</td>
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</tr>
<tr>
<td>Genetics Clinic</td>
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<tr>
<td>BC Pediatric Care Clinic - Yellow</td>
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<td><strong>Unable to Classify</strong></td>
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<tr>
<td>Outpatient Infusion Services</td>
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<tr>
<td>Radiology Outpatient</td>
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</tr>
<tr>
<td>SC Lab Outreach</td>
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</tr>
<tr>
<td>SC Occupational Therapy</td>
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</tr>
<tr>
<td>LAB Outpatient</td>
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<tr>
<td>NC Lab Outpatient</td>
<td>2</td>
</tr>
<tr>
<td>SC Lab Outpatient</td>
<td>6</td>
</tr>
</tbody>
</table>

Graph 2.

**Counts of patients on suppl. zinc that had serum zinc levels drawn**

- 60: no level drawn
- 33: one level drawn
- 6: two levels drawn
- 3: three levels drawn
- 0: four levels drawn
- 1: five levels drawn

25% of the serum zinc labs were drawn after 0600.

Graph 3.
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**Search Strategy and Results:**

**Question 1- Zinc and Absorption:** (February 14, 2011)


**Question 2- Zinc Deficiency:** (January 10, 2011)


**Question 3- Zinc and Failure to Thrive:** (January 10, 2011)


5 citations

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**Question 4- Zinc and Epidermolysis Bullosa**: (January 10, 2011)

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**Question 5 Zinc and Eczema**: (January 10, 2011)

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**Question Zinc and Harm-** (2/14/2011)

1.) Medline - PubMed ("Zinc/administration and dosage"[Major] OR "Zinc/adverse effects"[Major] OR ("Dietary Supplements/adverse effects"[Major] AND zinc[tiab])) AND ((odds AND ratio) OR benefi* OR harm* OR "Risk"[mesh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]) - limited to last 10 years

2.) MEDLINE- PubMed- search #2-((("Heavy Metal Toxicity" [Supplementary Concept]) OR "Metals, Heavy/poisoning"[Mesh]) AND "Zinc"[Mesh]) AND ("Dietary Supplements"[Mesh] OR supplement*)


4.) Heavy metal/contaminants MEDLINE - PubMed – (February 14, 2011) "Zinc/adverse effects"[MAJR] OR ("poisoning" [Subheading] OR "toxicity "[Subheading]) AND zinc[ti] AND (ingest* OR administration OR supplement*)

**Method Used for Appraisal and Synopsis:**

28 articles read are included in this review:

RevMan and Grade Pro were used to appraise and synthesize the studies. Meta analysis was performed using RevMan. For studies that did not report data that is used in meta analysis, a Critically Appraised Topic chart was prepared.

A narrative report on for the “harm” question is included in the summary.

**Results:** Of the 28 studies read, all but 5 had major limitations in the study design. See Risk of Bias Summary Chart. It is difficult to group studies for meta analysis because (a) varied age range of subjects studied, (b) varied dose of zinc supplement, (c) varied time between assessments, (d) varied methods used for assessment (serum v. plasma of zinc level and (e) varied outcomes studied varied among groups. However, sub groups were created to remove the variability due to age.

- To assess changes in zinc blood level there was high heterogeneity (I^2 > 95%) when studies could be grouped, except for children aged 3-6 years old. In general, the standard mean difference for blood zinc level showed no difference between supplemented subjects and those who received placebo. The strongest effect was seen in infants, but heterogeneity was high. (Figure 1)
- Wuehler (2008) demonstrated zinc supplementation as low as 3 mg/d increased plasma zinc concentrations (p> 0.001).
- To assess change in weight gain there was high heterogeneity. For the total group, the standard mean difference showed no difference between supplemented subjects and those who received placebo. Infants who were born small for gestational age had the greatest weight gain in response to zinc supplementation. (Figure 2)
- To assess change in height (length) gain for age there was high heterogeneity. For the total group, the standard mean difference showed no difference between supplemented subjects and those who received placebo. Infants who were born small for gestational age had the greatest gain in linear growth in response to zinc supplementation. (Figure 3)

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• The strongest relationship was found in change in weight for height (length) between those who received zinc supplement and those who received placebo. Five studies included this measure. The $I^2$ statistic was 0%. (Figure 4)
• There was one study that showed no difference in IQ at 9 years of age in subjects who received zinc supplementation as infants (Figure 5)
• In a study that compared zinc absorption in children on either a high or low phytate diet, dietary phytate did not appear to have an effect on plasma zinc or fecal zinc. (Figures 6 & 7)
• One study (Al-Gurairi, 2002) assessed the effect of supplemental zinc in the treatment of viral warts. There was high risk of bias for selection, detection, attrition bias. It is not clear if the study zinc dose was based on elemental zinc or zinc salt. 43% of subjects in the treatment group dropped out of the study and 50% of subjects in the placebo group dropped out. The study is included on the request of the team leaders. (Figure 8)
• It is difficult to assess harm, most reports are case reports. A summary follows:
  o Boreiko (2010) gives an overview of the difficulties of determining dietary/supplemental intake for adequate Zn nutrition. However he reports acute problems arise from a large single dose of >400mg elemental Zn per day is likely to cause nausea, vomiting and diarrhea. Chronic exposure of > 100 mg/d elemental zinc has a detrimental effect on Cu metabolism. He states “the risks of Zn deficiency are given higher priority than the risk of alterations in Cu metabolism”
  o DeOliveira (2009) report plasma iron and copper levels decreased when 22 mg/d elemental Zn was given over 12 weeks (healthy soccer players)
  o Dekker (2010) reported no change in hemoglobin when children aged 0-15 years were supplemented with 10-20 mg/d elemental zinc for 4-15 months.
  o Broun (1990) reported nonspecifically of sideroblastic anemia d/t bone marrow suppression in a person who ate zinc containing coins over a period of 12 years, and another person who took supplemental zinc for 2 years. No doses were given.
  o Finally, Wuehler (2008) stated no ill effects in children 12-30 months who took 10 mg/d zinc for 5 months.

Summary:

1. Based on guidance from the IOM and the WHO/UNICEF/IAEA/IZINC report, serum and/or plasma zinc is not a sensitive indicator of zinc status for individuals. It is useful on a population level. Obtaining serum zinc of the assessment of adequacy of zinc status is not recommended.

2. There is great heterogeneity in the data on supplemental zinc effect on plasma or serum zinc, weight change, height change. New research is very likely to change confidence in the effect seen by giving supplemental zinc.

3. There is stronger data that supports the effect of supplemental zinc on increasing weight for height (length), primarily in infants aged 1-6 months (only one study in this comparison included children aged 2-6 years (Walravens, 1983). New research is likely to change confidence in the effect seen by giving supplemental zinc.

4. Based on one study included in this review, dietary phytate did not change zinc absorption. However from the IOM report, dietary phytate is the major factor affecting the variability of zinc absorption. There is great uncertainty about the estimate of the effect from this study.

5. Questions surrounding zinc tablets available and getting the correct dose, now that zinc suspension is not available should be resolved.

6. Although LexiComp recommends 0.5-1 mg/kg as the dose for treating zinc deficiency in children, there is no maximum dose noted. The IOM report gives a Tolerable Upper Intake Level (UL). The UL is defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. The IOM used the activity of erythrocyte copper-zinc superoxide dismutase (ESOD) as a marker of an adverse effect of zinc intake. There was a consistent decrease in ESOD activity which is indicative of copper status.

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### UL by age

- 0-6 months: 4 mg/d of zinc
- 7-12 months: 5 mg/d
- 1-3 years: 7 mg/d
- 4-8 years: 12 mg/d
- 9-13 years: 23 mg/d
- 14-18 years: 34 mg/d
- Adults (> 19 years of age): 40 mg/d of zinc

The U/L value is based on reduction in erythrocyte copper-zinc superoxide dismutase activity. The emetic dose is 225-450 mg elemental zinc (National Academy of Science, 2001). Wuehler (2008) showed significant increases in plasma zinc in 1-3 year old children with doses as low as 3 mg/d. From this information, an upper limit on maximum zinc dose per age should be considered.
### References Included studies


Neither a zinc supplement nor phytate reduced maize nor their combination enhance growth of 6- to 12 month old Guatemalan infants.


Prasad, A. S., Beck, W. J. B., Kaplan, J., Chandrasekar, P. H., Ortega, J., Fitzgerald, J. T., & Swerdlo, P. Effect of zinc supplementation on
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<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Journal/Volume/Issue</th>
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<td>Wuehler, S.E., Sempértegui, F. &amp; Brown, K.H.</td>
<td>Dose-response trial of prophylactic zinc supplements, with or without copper, in young Ecuadorian...</td>
<td>...</td>
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</table>


Characteristics of excluded studies


Reason for exclusion: Used geometric means to compare data that cannot be used in meta analysis.


Reason for exclusion: 40% of subjects dropped out of the study. Drop outs were not described, not certain to which group they were assigned.

Other References


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Abdulhamid 2008

Methods
Prospective double blind placebo controlled study,

Participants
26 children ages 7 to 18 years old with CF exhibiting mild to moderate lung disease

Interventions
Treatment: daily dose of 30 mg of elemental Zn as Zn gluconate (15 mg/capsule) to group A for 12 consecutive months. Placebo: "placebo preparation"
The treatment and placebo groups were further stratified into zinc sufficient (zinc level > 90 mcg/dl and zinc deficient (≤ 89 mcg/dl) groups.
Participants in each group were followed every 3 months.

Outcomes
Zinc Adequate
No. of episodes requiring IV Antibiotics
No. of episodes requiring oral Antibiotics
%Compliance
Plasma Zinc Level

Notes
Exclusion criteria for the study included presence of acute severe infection at the time of enrollment, renal disease, severe hepatic disease, gall bladder disease, sickle cell disease (SCD), use of oral immunosuppressive drugs (steroids and non-steroid anti-inflammatory drugs), diuretics and Zn supplements.

Bias
Scholars' judgment
Support for judgment
Random sequence generation (selection bias) Low risk stated random, but did not elucidate
Allocation concealment (selection bias) Unclear risk
Blinding (performance bias and detection bias) Low risk supplements were made by outside lab
Incomplete outcome data (attrition bias) Low risk One participant dropped out of the zinc supplemented group.
Selective reporting (reporting bias) High risk Although all the groups had a normal zinc level based on the laboratory used for the study, the investigators chose ≤ 89 as deficient and ≥ 90 as sufficient. No mention of how those between 89 and 90 were handled.

Other bias Low risk

Al-Gurairi 2002

Methods
RCT

Participants
N=80 subjects with viral warts were recruited.
Inclusion criteria: > 15 warts, warts were recalcitrant after conventional treatment, and otherwise healthy.
N= 40 in treatment group; 4-50 years of age
N= 40 in control group; 7-37 years of age
Iran Teaching Hospital during May 1999 to April 2000.
Interventions
Zinc treated N=23 (4-50 years of age)
First group (treatment group) received oral Zn sulphate (10mg) in a dose of 10 mg/kg daily in three divided doses up to 600 mg/day.
The second group (control group) was given a placebo oral treatment in the form of glucose.

All subjects were instructed not to take any treatment other than prescribed in this trial. It is not clear if elemental zinc or zinc sulfate was dosed.

Outcomes
Serum zinc pre and one month post treatment.
The primary outcome measures were complete disappearance of the lesions without residual scarring.

Notes
The treatment continued for 2 months while the follow-up period lasted up to 6 months.
During treatment period the subjects were evaluated and examined every 2 weeks for evidence of partial or complete regression of their lesions, to record any adverse effects and to ensure that the patients were not using other treatments.

Bias
Scholar’s judgment
Support for judgment
Random sequence generation (selection bias) High risk Sequence was generated by odd numbered days treatment, even numbered days placebo.
Allocation concealment (selection bias) High risk Subjects were blinded to the type of treatment; observer was not.
Blinding (performance bias and detection bias) High risk Only 23 subjects of the group and 20 subjects of the second group completed the study and they only report on the completers. (57% and 50% completers respectively)
Incomplete outcome data (attrition bias) High risk In all subjects the serum level of Zn was low at the outset of the study.
Selective reporting (reporting bias) High risk
Other bias Low risk

Bin 2008
Methods RCT
Participants 36 adults (18-47 years) homozygous SCD.
Interventions Zinc group: 25 mg of zinc as the acetate salt orally 3 times per day for 3 months.
Outcomes Blood: plasma zinc concentration, nitrite and nitrate (NOx), antioxidant power, DNA oxidation products, lipid peroxidation products, soluble vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular

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adhesion molecule-1 (ICAM-1), and soluble E-selectin, as well as ex vivo study of nuclear factor-kappa B (NF-B)DNA binding, TNF-, IL-1, IL-2, and IL-2 receptor-alpha (IL-2R) mRNAs in isolated mononuclear cells (MNCs)

- Infections
- Acute vaso-occlusive pain crises

**Notes**
Excluded subjects who were non ambulatory, received > 6 transfusion/year or taking hydroxyurea, history of substance abuse, neurological or psychiatric deficits, + HIV, and + Hep B. Those taking zinc supplements

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s judgment</th>
<th>Support for judgment</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>technician blindly chose one of two identical bottles labeled as &quot;study drug&quot;. One bottle contained zinc the other did not.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>all persons were blinded including ID physicians who evaluate infections and hemologist who evaluated pain crises.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>They do not report on each subject for each lab analysis. They do not acknowledge missing subjects.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>For all laboratory analysis, they compare the supplemented group to themselves, not the placebo group. In other charts and text they compare SCD to healthy adults.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

**Berger 2005**

**Methods**  Prospective, RCT

**Participants**  Singleton breast-fed infants, age 4-7 months, from 24 communities of Que Vo, a rural & poor district NW of Hanoi in the Red River Delta in Vietnam. Approx 140 subjects per group.

**Interventions**  Treatment group: 10 mg zinc sulphate daily.
Control group: placebo
Supplements were placed in 2mL sweet-tasting syrup, in a similar coded bottle, given to mouth of infant via small plastic syringe. Supplements were given 7 days/wk during 6 months by trained field workers, one in each village. Supplementation was given between 0700-0900. No food/beverage given to infant after 2 hrs after treatment.

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Outcomes
Measurements include weight & height monthly from baseline to end of study.
Non-fasting blood samples collected in am at baseline & after 26 weeks to assess Hgb, serum ferritin & zinc.

Notes
Exclusion criteria: infants with chronic or acute illness, severe malnutrition or congenital abnormality, infants with Hgb <70g/l.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Infants were randomly assigned, following a computer-generated block randomized group allocation.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Computer generated.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Supplements were presented in similar coded bottles avoiding participants and health workers to differentiate between treatments. Supplements were coded with a letter at production &amp; the code-allocation kept secret until the end of the statistical analysis.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Discussed exclusion/drop-outs: Total of 915 included in study &amp; 784 infants completed 6 mo supplementation period. Dropout rate of 14.3% in each group. Drop-out reasons as follows: difficulty parents to bring infant daily to treatment place (93), refusal of 2nd blood sampling (38). Zinc group: N=247. refusal of blood sampling=18, hemoglobin&lt;70 grams/L=8, dropped out=20, absent at final evaluation=6 Placebo group: N=247. refusal of blood sampling=19, Hgb &lt; 70 grams/L=2, dropped out=15, absent at final evaluation=13 Per protocol analysis used. Treatment group (zinc) = 81% follow-up. Placebo group = 80% follow-up.</td>
</tr>
</tbody>
</table>

Selective reporting (reporting bias)            | Low risk          |
Other bias                                      | Low risk          |

Castillo-Duran 1995

Methods  RCT
Participants  80 infants born 38-41 week PMA ( < 10 percentile on the Lubchenco charts)
Interventions  Treatment group: 3 mg of zinc/day as the acetate salt (1mg Zn/ml).
Placebo: solution without zinc
Outcomes  Anthropometrics: weight, length, and OFC
Compliance  Laboratory: 30, 60, 140 and 180 days blood samples, hair samples, milk (formula or breast milk? not clear in methods.)

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

Notes
Excluded infants with congenital malformations, asphyxia, congenital infection, or if mother had preeclampsia or intrahepatic cholestasis. Infants with less than 50% compliance were excluded (12 infants, not certain to which group they were assigned.)

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for Judgment</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random assignment within blocks of 20</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Per protocol analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>They said they analyzed milk-</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>

Cole 2010

Methods
Cross-sectional study

Participants
292 children in Atlanta were recruited, 280 qualified for analysis. Mean age was 2.5 +/- 1.2 years.

Interventions
3 day food diary, hemoglobin, serum ferritin, zinc, copper and C-reactive protein. Growth by direct measure- length < 2 standing height > 2 years

Outcomes
Children with elevated C-reactive protein were excluded, as were children with sickle cell anemia, acute diarrhea or respiratory illness.

Notes
Non fasting blood draws
Zinc deficiency was defined pre hoc as a serum zinc concentration -10.7 micromole/L

<table>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Convenience sampling, age 12-60 months</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Cross-sectional study</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Cross-sectional study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Cross-sectional study</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Cross-sectional study</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

**deOliveria 2009**

**Methods**  
RCT single blinded

**Participants**  
Football players (N=47), on a junior soccer team in Rio de Janeiro 12-week, single-blinded, intervention trial with two randomly selected groups mean age 13 ± 0.4 years adolescent football (soccer) players,

**Interventions**  
Zinc Supplement (N=21) group one capsule daily 22 mg of zinc as zinc gluconate  
Placebo group (N=26) took one capsule daily of similar appearance containing maltodextrin.  
Blood and urine samples were obtained before (baseline) and after the 12-week of treatment.

**Outcomes**  
Lab results  
The objective of this study was to evaluate the effect of zinc supplementation on the antioxidant status, and on zinc, iron, and copper status in physically active male adolescents.

**Notes**

**Bias**  
Random sequence generation (selection bias)  
Allocation concealment (selection bias)  
Blinding (performance bias and detection bias)  
Incomplete outcome data (attrition bias)  
Selective reporting (reporting bias)  
Other bias

**Scholar’s Judgment**  
Unclear risk  
Unclear risk  
Unclear risk  
Low risk  
Low risk

**Support for Judgment**  
Authors state randomized, but do not give specifics  
Not described  
Subjects only were blinded  
All completed the study

**Dijkhuizen 2008**

**Methods**  
4 sites RCT

**Participants**  
Infant between 4-6 months of age. Sites (number) included Thailand (4), Vietnam, and Indonesia (2). Two other Indonesia dropped out, and data from these sites are not included in the analysis. (One had different study design and one decided not to participate.)  
There were four supplementation groups  
Zinc only, iron only, zinc+iron and placebo. This analysis includes zinc vs. placebo only.  
3 sites administered a high Vitamin A dose (one site 150 micrograms (50,000 international units), and 2 sites 300 micrograms (100,000 international units).

**Interventions**  
Treatment 10 mg of zinc as the sulfate salt  
Placebo: syrup with Vitamin C

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

supplementation was 5-7 days per week depending on site

Outcomes
- Anthropometrics; health, diet, lactation history; and possible adverse effects. Blood samples were taken at 6 months, venipuncture from 3 sites and heel-stick at one site.

Notes
- They used the NCHS growth charts and WHO charts, reporting on the NCHS charts so comparison can be made with other studies.

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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Not described in this article, but could find parent article</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>labels to supplement placed at product manufacturing site</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Not all sights obtained blood work, not all measured zinc concentrations.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>sponsored by UNICEF</td>
</tr>
</tbody>
</table>

Fischer Walker 2009

Methods
- Prospective, RCT

Participants
- Breast fed infants, age 5-6 months, permanent residents of selected villages in Bangladesh. Treatment group N=141, Control group N=140.

Interventions
- Treatment group: 20 mg elemental zinc & 1 mg riboflavin or control group: 1 mg riboflavin. Weekly supplementation given by trained community health worker (CHW) @ home visit. Measurements taken @ enrollment & q2 mo thereafter (6, 8, 10 & 12 mo age).

Outcomes
- Measurements included length, weight, and mid-upper arm circumference (MUAC)

Notes
- Exclusion criteria: low weight-for-age, severely anemic, or showed any signs of neurological disorder, physical handicap, or chronic illness affecting feeding, activity or cognitive development.

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<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Block randomization, stratified by length for age Z score using -2Z as cutoff.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Was not described in this article. The article stated that study design, population, trial profile &amp; methods were published previously.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Blinding was not described in detail for this study. There was no mention of CHW blinding. Measurements were taken by anthropometrist that was blinded to the supplementation allocation.</td>
</tr>
</tbody>
</table>

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Incomplete outcome data (attrition bias)  High risk  All calculations assumed a 10% loss to follow-up. Per protocol analysis used. Treatment group (zinc) = 86% follow-up. Control group = 89% follow-up.

Selective reporting (reporting bias)  Low risk

Other bias  Low risk

Hamadani 2001

Methods  RCT
Participants  Infants 1-6 months of age. N=213 (272 in the original group, 59 dropped out, do not know how many from each group.
Interventions  Treatment- 5 mg of elemental zinc as zinc acetate N= 104
Control- cellulose substance given as an identical syrup N=109
Outcomes  Bayley Scale MDI and PDI, Behavior rating, Home stimulation, socioeconomic status, and anthropometric measures
Notes

Bias  Scholar’s Judgment  Support for Judgment
Random sequence generation (selection bias)  Low risk  randomized, double-blind, controlled trial
Allocation concealment (selection bias)  Unclear risk  Did not state
Blinding (performance bias and detection bias)  Low risk  Double blind - families and the personnel who administered the Bayley were unaware of the group assignment.
Incomplete outcome data (attrition bias)  Low risk  Per protocol analysis, however, statistics were done to see if the loss may have biased the findings.
Selective reporting (reporting bias)  Low risk
Other bias  Low risk

Heinig 2006

Methods  RCT
Participants  Healthy term breast fed infants of mothers who planned to fully breast feed and not feed complementary foods before 4 months 4-10 months of age
85 enrolled, 70 completed the study
Power analysis performed need 70 total or 35 per group to see a difference in weight gain. Need > 1000 in each group to discern differences in performance on motor development tool used.

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Interventions
Treatment: 5 mg/d of zinc as zinc sulfate
Placebo

Outcomes
Growth, morbidity, motor development, plasma zinc, iron and copper, plasma ferritin, Hemoglobin and hematocrit
Record of complementary foods
5 major morbidity codes respiratory, diarrhea, otitis media, fever and other (all defined)
Motor development used the AIMS or the Alberta Infant Motor Scale.

Notes
Bias Scholar’s Judgment Support for Judgment
Random sequence generation (selection bias) Low risk Used a formal randomization tool the Moses-Oakford algorithm
Allocation concealment (selection bias) Low risk Lab assistant assigned labels and color coded. 4 colors assigned to reduce revealing accidentally
Blinding (performance bias and detection bias) Low risk Investigators and mothers only knew color assigned
Incomplete outcome data (attrition bias) Unclear risk Intention to treat analysis. however the statement is made: Because exclusion of infants who were excluded did not affect any results they were included in the analysis. Funny.

Selective reporting (reporting bias) High risk Did not report on plasma levels. Mothers would not allow blood draws.
Aims score tool would require > 1000 in each group to discern difference
Other bias Unclear risk

Henderson 1995

Methods
two way cross over, four phase design. Washout of 7 days between treatments.

Participants
10 healthy adult volunteers, 5 female. 20-23 years of age. 120% ideal body weight.

Interventions
Phase one: zinc acetate administered to subjects pre treated with famotidine (Pepcid) 40 mg oral suspension. Intra-gastric pH ≥5 (acetate high pH= AH)

Phase two: zinc oxide administered to subjects pretreated with a single oral does of famotidine 40 mg oral suspension. Intra-gastric pH ≥5/ (oxide high pH= OH)

Phase 3: zinc acetate administered to subjects with an intra-gastric pH ≤3 (acetate low pH= AL)

Phase 4: zinc oxide administered to subjects with an intra-gastric pH ≤3 (acetate low pH= OL)

All zinc doses were equivalent of 50 mg of elemental zinc. Subjects were fed a zinc controlled diet (18 mg zinc/d) on treatment day and the subsequent day for each treatment.

Outcomes
24 hour urine collection, intragastric pH monitoring for 4 hours after Zn administration, blood collection 1 hour after zinc

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**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

administration. *In vitro* dissolution tests of each salt at various pHs. Data collected: plasma zinc, urinary zinc.

### Notes

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>cross over design, served as own control</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Unclear, not certain of subjects could discern the treatments.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

**Hershkovitz 1999**

**Methods**

RCT with matching to 10 healthy controls

**Participants**

Infants aged 3-9 months with non organic failure to thrive,

**Interventions**

Recommended to discontinue breast feeding

Group A: 2 mg/kg/d elemental zinc as zinc acetate.

Group B: placebo- the solution used to dissolve the zinc as in group A

**Outcomes**

Lab values: Serum IGF-1, Serum IGFBP-3, and anthropometrics

**Notes**

Israel

Non fasting zinc determinations

<table>
<thead>
<tr>
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<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomization is not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Bottles were color coded.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>7 infants were excluded per protocol analysis</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>22% did not complete the protocol, not certain which group to which they were assigned.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Hettiarachichi 2008

Methods
RCT

Participants
821 adolescents age 12-16 years. All were treated for parasite infection prior to the study. Hemoglobin > 80 g/L. Zinc and iron deficiency are prevalent in the region of Sri Lanka where the study was completed.

Interventions
Each group received 2 capsules per school day of:
1: Iron- 50 mg/d as ferrous fumerate
2: Zinc- 14 mg/d as zinc sulphate
3: Combined iron and zinc as above
4: Placebo
Intervention was for 24 weeks.

Outcomes
Hbg concentration, serum zinc- skewed distribution, therefore log transformed.
Serum ferritin
Serum zinc
Growth using CDC/WHO weight for age and height for age z scores, BMI

Notes
Of 821 enrolled, 774 (91%) completed the study. Baseline outcomes were not different when completers were compared with non completers.

Bias
Random sequence generation (selection bias) Low risk Subjects were blinded by classroom in a double blind fashion
Allocation concealment (selection bias) Low risk Teachers gave the children the capsules, they were not aware of the group assignment
Blinding (performance bias and detection bias) Low risk Per protocol analysis. Teachers kept records of capsules taken and records were checked every 2 weeks for compliance to taking capsules. 58% of subjects took all doses (120), 32% received 110-119 doses and only 2% received < 100 doses. Resons for non completing- withdrawal and blood draw refusal, absent on day of blood draw.
Incomplete outcome data (attrition bias) Unclear risk Sample size was calculated at 180 per group; enrollment was inflated to 200 per group to account for drop outs. Completers met power requirements.
Selective reporting (reporting bias) Low risk
Other bias Unclear risk
Holtz 2005

Methods
- RCT

Participants
- Non-anemic but low iron stores (normal Hbg, but low ferritin) women 19-44 years of age.

Study was powered to detect a group difference of 8% zinc absorption by having 15 subjects per group (2 tailed test, SD 10.5, \( \alpha = 0.05 \), 80% power) However the SD from the first subjects completing the study were lower than above, the number of subjects was decreased. All were in the follicular stage of the menstrual cycle.

Interventions
- Addition of the test zinc salt to equal 40 mg zinc/ kg flour.

- Group one: Zinc oxide
- Group two: Zinc oxide + Na\(_2\)EDTA
- Group Three: Na\(_2\)ZnEDTA
- Group Four: ZnSo4

Outcomes
- urine zinc,
- fractional absorption of zinc (calculated using the tracer to tracee method)
- serum zinc
- hemoglobin
- C-reactive protein

Notes
- They did not meet power for any group, but justified it by saying the SD of the first groups was lower than the population they based the power analysis upon. They state a smaller number of subjects is justified for this reason.

Bias | Scholar’s judgment | Support for judgment
--- | --- | ---
Random sequence generation (selection bias) | Low risk |  
Allocation concealment (selection bias) | Low risk |  
Blinding (performance bias and detection bias) | Unclear risk | Blinding not described at all. Not certain if lab personnel knew which groups the specimens they handled were from. 
Incomplete outcome data (attrition bias) | High risk | It appears they did a power analysis, and then did not pay attention to it. They explained their way around it. 
Selective reporting (reporting bias) | Low risk |  
Other bias | Unclear risk | 2 samples were lost due to electrical failure in the laboratory, both from the zinc oxide group.
Kennedy 2010

**Methods**
prospective observational study receiving a habitual maize-based high-phytate diet; these children served as their own controls

**Participants**
10 Malawian children, ages 2-5 years, at risk for zinc deficiency and receiving a habitual maize-based high-phytate diet. Power analysis was done.

**Interventions**
each child received 170 micrograms IV labeled zinc followed by marking and collecting stool and keeping weighed food records

Subjects were given phytate-reduced maize for 40 days- enzymatic techniques (phytase) to reduce phytate were used. Food samples were analyzed. Phytate was reduced in the flour by 96%.

Dietary phytate was reduced by 65%

**Outcomes**
Fecal zinc, clean void urine, pre and post 40 days of phytate reduction

**Notes**
The primary limitation of the study is that concomitant dietary zinc absorption data are not available in these children, which would allow for interpretation of EFZ with respect to net zinc retention. Because they did not measure dietary zinc absorption, they cannot be certain whether EFZ was inappropriately high.

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<tbody>
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<td>Random sequence generation</td>
<td>High risk</td>
<td>not randomized</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High risk</td>
<td>all received the low phytate flour</td>
</tr>
<tr>
<td>Blinding</td>
<td>High risk</td>
<td>no intention to blind</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk.</td>
<td>not a robust design,</td>
</tr>
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If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
The primary limitation of the study is that concomitant dietary zinc absorption data are not available in these children, which would allow for interpretation of EFZ with respect to net zinc retention. Because they did not measure dietary zinc absorption, they cannot be certain whether EFZ was inappropriately high.

### Bias

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<tr>
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<td>Unclear risk</td>
<td>not a robust design,</td>
</tr>
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</table>

### Methods

- **cross sectional-cohort**

### Participants

- 60 Guatemalan schoolchildren between ages 7.5 - 12 years

### Interventions

- Children were fed low-phytate maize, or 1 of 2 control maizes for 10 weeks
  - Treatment 1 - low phytate maize - 60% less phytate
  - Treatment 2 - wild-type isohybrid of maize fed in treatment 1
  - Treatment 4 - locally grown maize

### Outcomes

- Zinc intake, phytate:zinc ratio; plasma zinc; fractional absorption of zinc; total absorbed zinc

### Notes

- Study conducted in Guatemala, but analysis was done in Colorado

### Support for Judgment

- Not clear "families were approached for participation in the basis of the age of their apparently healthy children (6-11 years), their willingness to allow their children to participate in the study, and the willingness of the entire family to consume the study maize."
- Participants "probably distinguished the local control maize;" A power analysis was performed. Need 20 subjects per intervention group.
- Investigators in Colorado were blinded to the treatment group assignments
- One dropout, intention to treat analysis
- The data they collected did not show what they expected. They did a post hoc analysis to report a significant finding.
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

### Mazariegos 2010

**Methods**
Blinded RCT

**Participants**
Infants 6-12 months of age N=420 Did power analysis based on linear growth velocity (6% increase in linear growth rate). The study was also powered to detect an interaction between the zinc supplement and low phytate maize to determine whether the effect of the zinc supplement differed between the 2 maize treatment groups. They recruited 412 infants between 2004-2006 and 384 subjects completed the study.

**Interventions**
- Treatment one: Low phytate ~ 80% reduced
- Treatment two: High phytate ~ 710 mg/100 g
  
  \[ [Zn] = 2.6 \text{ mg/100 g} \] of both types of maize (this is 50% higher than most maize)
- Each maize treatment group was further randomized to zinc treatment groups
- Treatment one: Zinc 5 mg/d
- Treatment tow: Placebo
  
  (mother had to score and break the tablet and administer 0.5 tablet per day. She also had to assure the tablet was dissolved and swallowed)

**Outcomes**
- Primary outcome linear growth velocity
- Secondary outcomes: other growth measures, neurodevelopment and prevalence and incidence of infectious disease morbidity.

**Notes**
The study was done in Guatemala, and analyzed in Colorado

Hypothesis one: low phytate maize would increase infant linear growth velocity between 6 and 12 months independent of the receipt of a zinc supplement.

Hypothesis two: a small zinc supplement (5 mg/d) would increase infant linear growth velocity independent of the type of maize eaten.

### Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>permuted blocks of 6 for both flour and zinc.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Each sack of flour was color coded. Families were assigned a color. Only flour with that colored label was distributed.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Only one author who over saw grain quality was not blinded. He did not see families.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Pongcharoen 2011

Methods
Follow-up study 1998-1999 original- the original was a randomized 2X2 factorial, double blind placebo controlled trial. Follow-up cross sectional study conducted from August 2007 to January 2008

Participants
560 children aged 9 y or 92% of those who had participated in a RCT involving 4 groups who received daily iron, zinc, iron plus zinc or a placebo 2 ml dose for 6 months.
Group 1- 5 grams/L iron as iron sulfate
Group 2- 5 grams /L zinc as zinc sulfate
Group 3- 5g/L iron as iron sulfate and 5 grams /L zinc as zinc sulfate
Group 4- Placebo
Administered by parents using a oral medication syringe, given between meals. Compliance monitored by village health volunteers. Monthly measurement of syrup administered

Interventions
Wechsler intelligence Scale for Children-Third Edition (Thai Version), the Ravens Colored Progressive Matrices, and school performance tests. General linear mixed models were used to assess long-term effects

Outcomes
Full IQ scale, serum zinc, weight z-score, length z-score

Notes
Went to original study, to get enrollment information see: Wasantwisut 2006

Bias
Random sequence generation (selection bias) Low risk Randomized 2X2 factorial process. Power calculation was done to detect a difference in length for age z-score of 0.15. Stratified by age and sex.
Allocation concealment (selection bias) Low risk Random numbers generated by statistician not involved in the study. Syrups were made and labeled by a pharmacy not other wise involved. allocation codes were kept at the UNICEF office until the end of data analysis
Blinding (performance bias and detection bias) Low risk clinical psychologists were unaware of the child's intervention group
Incomplete outcome data (attrition bias) Low risk This is a 9 year follow up study. Located 562 of the original 609 children for follow-up testing (92%)
Selective reporting (reporting bias) Low risk both WISC-III and Ravens CPM tests were adm by clinical psychologists using standard protocol
Other bias Low risk

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
Taneja 2009

**Methods**
- RCT

**Participants**
- 2052 hospital born term (> 37 weeks) infants with BW \(\leq 2500\) g

**Interventions**
- Treatment: zinc 5 mg/d- 2 weeks of age to 6 months and 10 mg/d > 6 months
- Placebo: tablets with out zinc
- Parents were given zinc sulfate tablets or placebo tablets. Instructed to dissolve in 5 ml of breast milk for young infants or breast milk or water for older infants.
- Sample size was estimated on the reduction of all cause hospitalizations in this age group. Sample size required 2000 infants.

**Outcomes**
- Monthly visits for compliance, every three months for measures blood work at conclusion only 15 percent of infants at start and stop of study
- all cause hospitalizations
- prevalence of diarrhea
- acute lower respiratory tract infections
- visits to health care providers
- weights and lengths at 3, 6, 9 and 12 months.

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>permuted blocks of fixed length of 20</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>statistician not involved with the study created randomization list and labeled the supplements</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Per protocol analysis, only 15% of infants had blood work drawn at the beginning and end of the study.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

**Tran 2004**

**Methods**
- Cross over design

**Participants**
- 8 healthy adults (3 men and 5 women) Age 33.8 ± 9.8 years

**Interventions**
- Aqueous zinc sulfate was administered (one pair per phase). Three week washout between phases
- Phase 1: 2 and 5 mg

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Phase 2: 10 and 15 mg
Phase 3: 20 and 30 mg
Each solution was administered over a 15 week period and

**Outcomes** Fractional absorption of zinc and absorbed zinc

**Notes** Goal was to find dose-response data for the absorption of zinc from a range of oral doses to assist in establishing dosage guidelines for short term relatively high dose zinc supplementation.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>&quot;Phase' of zinc supplementation was randomized</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Power analysis performed- 8 subjects</td>
</tr>
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<td>Selective reporting (reporting bias)</td>
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<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td></td>
</tr>
</tbody>
</table>

**Walravens 1983**

**Methods** pair matched cohort

**Participants** 28 pairs, Hispanic American children aged 2-6 years

**Interventions** Treatment: 5 mg of zinc as zinc sulphate 2 times per day for one year

Placebo: cherry flavored syrup for one year

**Outcomes** Anthropometrics, Dietary evaluation, Pre and Post plasma zinc levels, Plasma copper, s. albumin, total protein, cholesterol, alkaline phosphatase, and vitamin A.

**Notes** Handling of drop outs "When a member of a pair defaulted, the other was re-matched with the first suitable candidate (either a compatible participant already waiting to be paired or a new entrant.)"

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>&quot;The first member of the pair was assigned randomly to either the zinc supplement or placebo&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment- do not state how random occurred.</td>
</tr>
</tbody>
</table>

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**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

Blinding (performance bias and detection bias) | Unclear risk | Not stated
Incomplete outcome data (attrition bias) | High risk | Per protocol analysis, dropouts were not included
Selective reporting (reporting bias) | Low risk | Low risk
Other bias | Low risk | Low risk

**Wasantwisut 2006**

**Methods**
RCT

**Participants**
560 4-6 month old children from rural Thai villages. Healthy

**Interventions**
2 ml/d dose for 6 months.
- Group 1- 5 grams/L iron as iron sulfate
- Group 2- 5 grams/L zinc as zinc sulfate
- Group 3- 5g/L iron as iron sulfate and 5 grams/L zinc as zinc sulfate
- Group 4- Placebo
Administered by parents using a oral medication syringe, given between meals. Compliance monitored by village health volunteers. Monthly measurement of syrup administered

**Outcomes**
Anthropometrics- length for age z-score, weight for age z-score and weight for length z-score.

**Notes**
Randomized 2X2 factorial process. Power calculation was done to detect a difference in length for age z-score of 0.15. Stratified by age and sex.

Random numbers generated by statistician not involved in the study. Syrups were made and labeled by a pharmacy not otherwise involved. allocation codes were kept at the UNICEF office until the end of data analysis

Blood only obtained from mother's who consented to blood draws

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Weuhler 2008

Methods
Double blind RCT. Participants were stratified by age (12–20 or 21–30 mo old) and sex. Children in each of the study groups consumed 1 of 5 daily supplements containing 3, 7, or 10 mg Zn as zinc sulfate, 10 mg Zn 0.5 mg Cu as copper sulfate, or placebo per 5 mL of flavored syrup. The randomization lists for each of these strata were generated independently by using a fixed block randomization procedure.

Participants
631 Ecuadorian (non-anemic) children aged 12–20 mo old LAZ < -1.3
21-29 mo old LAZ < -1.5 as compared to the 1978 WHO data and NCHS international data. Hemoglobin > 10.5/dl
Growth response to zinc occurs among populations with LAZ < -1.5

Interventions
Treatment 1: 3 mg of zinc as zinc sulfate daily
Treatment 2: 7 mg of zinc as zinc sulfate daily
Treatment 3: 10 mg Zn as zinc sulfate, daily
Treatment 4: 10 mg Zn as zinc sulfate and 0.5 mg Cu as copper sulfate daily
Treatment 5: placebo as flavored syrup.

Outcomes
Measure the effects of different doses of supplemental zinc on the plasma zinc concentration, morbidity, and growth of young children; to detect any adverse effects of 10 mg supplemental Zn on markers of copper or iron status; and to determine whether any adverse effects are alleviated by providing copper with zinc.

Notes
Bias
Random sequence generation (selection bias) Low risk
Allocation concealment (selection bias) Unclear risk
Blinding (performance bias and detection bias) Low risk
Incomplete outcome data (attrition bias) High risk
Selective reporting (reporting bias) Low risk
Other bias Low risk

Support for Judgment
Fixed block randomization schedules, configured independently for each strata.
Not stated
Supplements compounded and labeled at central pharmacy
Used subsets of groups for obtaining blood levels of Zn and Cu. The sets from which final blood samples were obtained were randomly determined. Per protocol analysis.

Yip 1985

Methods
Survey

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Participants

Interventions
First Study:
- Diet history taken by physician or nurse
- 10 ml of non fasting venous blood for hemoglobin, MCV, serum ferritin, erythrocyte protoporphyrin as serum iron/iron binding capacity (Fe/TIBC) serum zinc and serum copper.

Second study:
- Treatment: 291 subjects were randomized to receive iron or placebo using and odd/even day schedule.
- Medication was labeled by code 30 mg/kg/d elemental ion for 3 months.
- Blood work was repeated in compliant children at 15 mo visit.

Outcomes
Relationship between dietary factors and results of laboratory tests at 12 months of age.
Compliance to iron/placebo administration.

Bias | Scholar’s Judgment | Support for Judgment
--- | --- | ---
Random sequence generation (selection bias) | High risk | odd/even day is not an appropriate way to randomize
Allocation concealment (selection bias) | Low risk |
Blinding (performance bias and detection bias) | Low risk |
Incomplete outcome data (attrition bias) | High risk |
Selective reporting (reporting bias) | Low risk |
Other bias | Low risk |

Zemel 2002

Methods
RCT

Participants
42 children (20 girls and 22 boys) pre-pubertal children aged 4-10 with sickle cell disease.

Interventions
Treatment : 10 mg/d of zinc in cherry syrup (5 ml/d) N=20
Placebo: cherry syrup without zinc (5 ml/d) N=22.
Evaluations occurred at 3,6 and 12 months after supplementation began.

Outcomes
Anthropometrics- height and sitting height, weight, upper arm circumference skin folds at biceps, triceps, sub scapular, and supra iliac sites in triplicate- compared to NCHS charts
Sexual maturation
Body Composition
Dietary Intake
Fasting blood samples for: plasma zinc

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Compliance: calendars, return syrup containers every three months, interview. ≥75% of the time, < 75% of time or uncertain were cutoffs.

Notes
Stature at beginning of study < 2 SD below the mean, they did not report standard deviation on plasma zinc scores, so cannot use this data.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholar’s Judgment</th>
<th>Support for Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>They used a random number table to establish an unbiased order of contacting and recruiting subjects. They were randomized again after study enrollment.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Research pharmacy prepared the syrups.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Younger taller girls and shorter boys were over represented. 38 of 42 subjects completed the study. A per protocol analysis was done. The four children who did not complete the study had significantly lower height for age z-scores.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Some children were taking zinc supplements and were asked to refrain for 1 month prior to study enrollment- not sure which children they were maybe the taller girls?</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of excluded studies

Silva 2006

**Reason for exclusion**

40 percent dropout rate. No description of reason for drop outs or from which group they were from.

López de Romaña 2003

**Reason for exclusion**

Use geometric means for analysis. No numbers were reported, only graphs.
# Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

**Author(s)** Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina Gutierrez, and Jackie Bartlett

**Date:** 2011-05-27

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma or Serum Zinc by Age Group (follow-up 2-12 months; measured with: Serum of Plasma zinc (mcg/dl) ; range of scores: 30-200; Better indicated by higher values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>randomized trials¹</td>
<td>no serious limitations²</td>
<td>serious³</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>539</td>
<td>565</td>
</tr>
</tbody>
</table>

| Plasma or Serum Zinc by Age Group - Infants (follow-up 6-12 months; range of scores: 30-200; Better indicated by higher values) |
| 4 | randomized trials | serious⁴ | very serious⁵⁶ | no serious indirectness | no serious imprecision | none | 439 | 461 | - | SMD 1.13 higher (0.22 to 2.05 higher) | ⊕ΟΟΟ | VERY LOW | CRITICAL |

| Plasma or Serum Zinc by Age Group - > 12 months and < 6 years (follow-up 1 years; range of scores: 30-200; Better indicated by higher values) |
| 1 | randomized trials | serious⁵ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 32 | 32 | - | SMD 0.22 lower (0.71 lower to 0.27 higher) | ⊕ΟΟΟ | MODERATE | CRITICAL |

| Plasma or Serum Zinc by Age Group - > 6 years (follow-up 3-12 months; measured with: change from baseline; Better indicated by higher values) |
| 2 | randomized trials | serious⁶⁷ | very serious⁸ | no serious indirectness | no serious imprecision | none | 33 | 39 | - | SMD 0 higher (0.46 lower to 0.46 higher) | ⊕ΟΟΟ | VERY LOW | CRITICAL |

| Plasma or Serum Zinc by Age Group - Small for Gestational Age (follow-up 180 days; measured with: change from baseline; Better indicated by higher values) |
| 1 | randomized trials | serious⁹ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 35 | 33 | - | SMD 0.16 higher (0.32 lower to 0.63 higher) | ⊕ΟΟΟ | MODERATE | CRITICAL |

| Change in Weight for Height z score (follow-up 6-13 months; measured with: NCHS growth chart; Better indicated by higher values) |
| 5 | randomized trials | no serious limitations⁶ | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1073 | 1094 | - | MD 0.1 higher (0.04 to 0.16 higher) | ⊕⊕⊕⊕ | HIGH | CRITICAL |

¹ Most studies are in the infant group.
² Incomplete outcome data is the most frequent bias in studies.
³ For the series of all studies that reported changes in plasma or serum zinc the I² = 96%.
⁴ Various zinc doses (5-10 mg/d) and various times of follow-up.
⁵ Some report serum or plasma zinc levels, other report change in serum or plasma zinc level.
⁶ number of drop outs not stated, nor was the group assignment of drop outs stated. It was a per protocol analysis, drop outs were not included in the analysis.

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

zinc dose varied from 15 mg/d- 22 mg/d.
deOliveria was teenage (~13 years) football (soccer) players in Brazil, the Abdulhamid study was 7-18 year olds with mild to moderate cystic fibrosis.

Per protocol design

Author(s): Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina Gutierrez, Jackie Bartlett

Date: 2011-02-22

Question: Should Zinc supplement be used in Pediatrics?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>No of patients</td>
</tr>
<tr>
<td>Design</td>
<td>Limitations</td>
</tr>
</tbody>
</table>
| Wart remained at 2 months (follow-up 2 months; physical exam)

1. randomized trials
2. serious
3. no serious inconsistency
4. no serious indirectness
5. serious
6. none

7. 3/23 (13%)
8. 20/20 (100%)
9. OR 0 (0 to 0.09)
10. -
11. ⊕⊕ΟΟ LOW IMPORTANT

| Change in Height for age (follow-up 4-12 months; measured with: change in length or height in centimeters; range of scores: 0-10; Better indicated by higher values)

6. randomized trials
7. serious
8. very serious
9. no serious indirectness
10. serious
11. none

12. 453
13. 467
14. -
15. MD 0.43 higher (0 to 0.87 higher)
16. ⊕ΟΟΟ VERY LOW CRITICAL

| Change in Weight for age (follow-up 4-12 months; Better indicated by higher values)

5. randomized trials
6. serious
7. very serious
8. no serious indirectness
9. serious
10. none

11. 425
12. 439
13. -
14. MD 0.12 higher (0.02 lower to 0.25 higher)
15. ⊕ΟΟΟ VERY LOW CRITICAL

| Mid Upper Arm Circumference (follow-up 4-12 months; Better indicated by higher values)

3. randomized trials
4. serious
5. no serious inconsistency
6. no serious indirectness
7. no serious imprecision
8. none

9. 223
10. 222
11. -
12. MD 0.16 higher (0.36 lower to 0.67 higher)
13. ⊕⊕ΟΟ MODERATE IMPORTANT

| Number underweight at 12 months

1. randomized trials
2. serious
3. no serious inconsistency
4. no serious indirectness
5. no serious imprecision
6. none

7. 506/976 (51.8%)
8. 484/947 (51.1%)
9. OR 1.03 (0.86 to 1.23)
10. 7 more per 1000 (from 38 fewer to 51 more)
11. ⊕⊕ΟΟ MODERATE

1. Algurairi 2002, Iran
2. sequence generation by odd and even days
3. Investigator not blinded to treatment group allocation
4. Small study

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Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu


For the Heinig study, mothers of infants refused blood draws.

Wide heterogeneity

Three studies are breast feed infants and 3 are children. No application to older children.

The effect was only seen in one small study Mozaffari-Khosravi 2008, otherwise, little or no difference seen.


Most used per protocol analysis

One infant and two child studies

Only 15% of subjects had serum levels of zinc determined.

Author(s): Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina Gutierrez and Jackie Bartlett

Date: 2011-02-22

Question: Low Phytate v High Phytate for zinc absorption.

<table>
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</thead>
<tbody>
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<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>Quality</td>
<td>Importance</td>
</tr>
</tbody>
</table>

**Fecal zinc microgram/kg/d (Better indicated by lower values)**

1. randomized trials
   - serious
   - no serious inconsistency
   - no serious indirectness
   - serious
   - none

   10 10 -

   MD 0.4 higher (16.32 lower to 17.12 higher)

   ⊕⊕ΟΟ

   LOW

**Plasma zinc µmol/L (Better indicated by lower values)**

1. randomized trials
   - serious
   - no serious inconsistency
   - no serious indirectness
   - serious
   - none

   10 10 -

   MD 0.5 higher (1.76 lower to 2.76 higher)

   ⊕⊕ΟΟ

   LOW

   IMPORTANT

* Cross over design of only 10 patients
**Synopsis:** Office of Evidence Based Practice – Specific Care Question Zinc

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Incomplete outcome data</th>
<th>Selective reporting (reporting bias)</th>
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<tbody>
<tr>
<td>Abdulhamid 2008</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Al-Gurairi 2002</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Bao 2008</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Berger 2005</td>
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<td>+</td>
<td>+</td>
<td>-</td>
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<td>Castillo-Duran 1995</td>
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<tr>
<td>Cole 2010</td>
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<td>?</td>
<td>?</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>deOliveria 2009</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Dijkhuizen 2008</td>
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<tr>
<td>Fischer Walker 2009</td>
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<td>+</td>
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<tr>
<td>Hamadani 2001</td>
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<td>+</td>
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<td>Henderson 1995</td>
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<tr>
<td>Hershkovitz 1999</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Hettiarachchi 2008</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Holtz 2005</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Kennedy 2010</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Mazariegos 2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Mazariegos 2010</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Pongcharoen 2011</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Forest Plots

**Figure 1.** Zinc supplement vs. placebo: Plasma or serum zinc by age group

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>1.1.1 Infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger 2005</td>
<td>23.07</td>
<td>4.6</td>
<td>15.79</td>
<td>1.6</td>
</tr>
<tr>
<td>Taneja 2009</td>
<td>100.2</td>
<td>41.9</td>
<td>73.3</td>
<td>22.5</td>
</tr>
<tr>
<td>Walravens 1983</td>
<td>71</td>
<td>14</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>Wasantwisut 2006</td>
<td>16.7</td>
<td>5.2</td>
<td>9.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>439</td>
<td>51.4%</td>
<td>461</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.84; Chi² = 100.41, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.43 (P = 0.02)

1.1.2 > 12 months and < 6 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walravens 1983</td>
<td>71</td>
<td>14</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>12.5%</td>
<td>32</td>
<td>-0.22</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)

1.1.3 > 6 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdulhamid 2008</td>
<td>6.1</td>
<td>9.4</td>
<td>8.6</td>
<td>22</td>
</tr>
<tr>
<td>deOliveira 2009</td>
<td>18.7</td>
<td>35</td>
<td>16.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>23.6%</td>
<td>39</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

1.1.4 Small for Gestational Age

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castillo-Duran 1995</td>
<td>10.5</td>
<td>14</td>
<td>35</td>
<td>8.9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>35</td>
<td>12.5%</td>
<td>33</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

Total (95% CI) 539 500 100.0% 0.57 [-0.12, 1.26]

Heterogeneity: Tau² = 0.93; Chi² = 170.60, df = 7 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Chi² = 6.74, df = 3 (P = 0.08), I² = 55.5%
### Figure 2. Zinc Supplement vs. Placebo: Change in weight for age

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger 2005</td>
<td>23.07</td>
<td>4.6</td>
<td>190</td>
<td>16.79</td>
<td>1.6</td>
<td>195</td>
<td>13.3%</td>
<td>2.10 [1.86, 2.35]</td>
<td></td>
</tr>
<tr>
<td>Thanja 2009</td>
<td>100.2</td>
<td>41.9</td>
<td>151</td>
<td>73.3</td>
<td>22.5</td>
<td>160</td>
<td>13.3%</td>
<td>0.61 [0.59, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Waseem 2008</td>
<td>16.7</td>
<td>5.2</td>
<td>66</td>
<td>9.8</td>
<td>1.0</td>
<td>66</td>
<td>12.7%</td>
<td>1.60 [1.38, 2.22]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>429</td>
<td></td>
<td></td>
<td>429</td>
<td></td>
<td>1.57 [0.67, 2.46]</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>0.60</td>
<td></td>
<td></td>
<td>59.61</td>
<td></td>
<td></td>
<td>2 (P = 0.00001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 3.43 (P = 0.0000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **12-16 months** |      |    |       |      |    |       |        |                                        |                                        |
| **Weight Loss**   | 72   | 14| 32    | 74   | 13| 32    | 12.3%  | 0.22 [-0.71, 0.27]                      |                                        |
| **Total**         |      |    | 48    |      |    | 48    |        | 0.22 [-0.71, 0.27]                      |                                        |
| **Heterogeneity** | Not applicable |
| **Test for overall effect Z = 0.87 (P = 0.38)** | |

| **18-23 years**   |      |    |       |      |    |       |        |                                        |                                        |
| **Weight Loss**   | 11.68| 1.24| 201   | 16.18| 1.49| 181   | 13.3%  | 1.32 [1.10, 1.54]                      |                                        |
| **Total**         |      |    | 382   |      |    | 382   |        | 1.32 [1.10, 1.54]                      |                                        |
| **Heterogeneity** | Not applicable |
| **Test for overall effect Z = 1.65 (P = 0.10)** | |

| **6 years**       |      |    |       |      |    |       |        |                                        |                                        |
| **Weight Loss**   | 0.1  | 0.4| 12    | 8.6  | 2.2| 13    | 10.8%  | -0.14 [-0.93, 0.64]                     |                                        |
| **Total**         |      |    | 37    |      |    | 37    |        | -0.14 [-0.93, 0.64]                     |                                        |
| **Heterogeneity** | Tau² = 0.00; Chi² = 10.0; df = 1 (P = 0.66); P = 0% |
| **Test for overall effect Z = 0.00 (P = 1.00)** | |

| **Small for Gestational Age** |      |    |       |      |    |       |        |                                        |                                        |
| **Weight Loss**   | 10.5 | 1.4| 36    | 8.9  | 1.6| 33    | 12.4%  | 0.16 [-0.32, 0.63]                      |                                        |
| **Total**         |      |    | 708   |      |    | 708   |        | 0.16 [-0.32, 0.63]                      |                                        |
| **Heterogeneity** | Not applicable |
| **Test for overall effect Z = 0.84 (P = 0.52)** | |

If you have questions regarding this Specific Care Question – please contact bnewell@c mh.edu
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

---

**Figure 3** Zinc Supplement vs. Placebo: Change in height (length) for age

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.4.1 Change height</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger 2005</td>
<td>-0.37</td>
<td>0.39</td>
<td>191</td>
<td>-0.42</td>
<td>0.46</td>
<td>195</td>
<td>9.8%</td>
<td>0.12 [-0.08, 0.32]</td>
<td></td>
</tr>
<tr>
<td>deOliveria 2009</td>
<td>158</td>
<td>10</td>
<td>21</td>
<td>161</td>
<td>9</td>
<td>26</td>
<td>4.8%</td>
<td>-0.31 [-0.89, 0.27]</td>
<td></td>
</tr>
<tr>
<td>Dijkhuizen 2008</td>
<td>7.5</td>
<td>1.7</td>
<td>625</td>
<td>7.6</td>
<td>1.7</td>
<td>614</td>
<td>10.9%</td>
<td>-0.06 [-0.17, 0.05]</td>
<td></td>
</tr>
<tr>
<td>Fischer Walker 2009</td>
<td>70.9</td>
<td>2.8</td>
<td>141</td>
<td>71</td>
<td>2.6</td>
<td>140</td>
<td>9.3%</td>
<td>-0.04 [-0.27, 0.20]</td>
<td></td>
</tr>
<tr>
<td>Hamadani 2001</td>
<td>-2.3</td>
<td>1</td>
<td>97</td>
<td>-2.4</td>
<td>1</td>
<td>101</td>
<td>8.7%</td>
<td>0.10 [-0.18, 0.38]</td>
<td></td>
</tr>
<tr>
<td>Heinig 2006</td>
<td>8.9</td>
<td>1</td>
<td>33</td>
<td>8.9</td>
<td>1.1</td>
<td>37</td>
<td>6.0%</td>
<td>0.00 [-0.47, 0.47]</td>
<td></td>
</tr>
<tr>
<td>Hershkovitz 1999</td>
<td>-1.71</td>
<td>1.08</td>
<td>14</td>
<td>-1.3</td>
<td>1.38</td>
<td>11</td>
<td>3.2%</td>
<td>-0.33 [-1.12, 0.47]</td>
<td></td>
</tr>
<tr>
<td>Mazariogos 2010</td>
<td>-2.57</td>
<td>1.1</td>
<td>188</td>
<td>-2.52</td>
<td>1.13</td>
<td>196</td>
<td>9.8%</td>
<td>-0.04 [-0.24, 0.16]</td>
<td></td>
</tr>
<tr>
<td>Wairavens 1983</td>
<td>6.73</td>
<td>0.63</td>
<td>20</td>
<td>6.12</td>
<td>0.7</td>
<td>20</td>
<td>4.1%</td>
<td>0.90 [0.24, 1.55]</td>
<td></td>
</tr>
<tr>
<td>Wasantwisut 2006</td>
<td>-1.0</td>
<td>0.9</td>
<td>151</td>
<td>-0.99</td>
<td>0.86</td>
<td>153</td>
<td>9.5%</td>
<td>-0.01 [-0.24, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Weuhler 2008</td>
<td>0.15</td>
<td>0.29</td>
<td>52</td>
<td>0.11</td>
<td>0.32</td>
<td>56</td>
<td>7.2%</td>
<td>0.13 [-0.25, 0.51]</td>
<td></td>
</tr>
<tr>
<td>Weuhler 2008</td>
<td>0.05</td>
<td>0.33</td>
<td>54</td>
<td>0.44</td>
<td>0.32</td>
<td>56</td>
<td>6.8%</td>
<td>-1.19 [-1.60, -0.79]</td>
<td></td>
</tr>
<tr>
<td>Zemel 2002</td>
<td>-0.35</td>
<td>1.03</td>
<td>18</td>
<td>-0.23</td>
<td>1.14</td>
<td>20</td>
<td>4.3%</td>
<td>-0.11 [-0.75, 0.53]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>1605</td>
<td></td>
<td></td>
<td>1625</td>
<td>94.3%</td>
<td>-0.06 [-0.22, 0.10]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.05; Chi² = 44.41, df = 12 (P < 0.0001); I² = 73%
Test for overall effect: Z = 0.76 (P = 0.45)

**1.4.4 Small for Gestational Age**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castilo-Duran 1995</td>
<td>-0.66</td>
<td>0.79</td>
<td>35</td>
<td>-1.47</td>
<td>1.28</td>
<td>33</td>
<td>5.7%</td>
<td>0.76 [0.26, 1.25]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>35</td>
<td></td>
<td></td>
<td>33</td>
<td>5.7%</td>
<td>0.76 [0.26, 1.25]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 3.61 (P = 0.003)

Total (95% CI) 1640 1658 100.0% -0.02 [-0.18, 0.15]

Heterogeneity: Tau² = 0.06; Chi² = 54.28, df = 13 (P < 0.00001); I² = 76%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Chi² = 9.61, df = 1 (P = 0.002), I² = 89.6%

---

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

**Figure 4** Zinc Supplement vs. Placebo: Change in weight for height (length) z-score

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger 2005</td>
<td>-0.96</td>
<td>0.51</td>
<td>191</td>
<td>-1.13</td>
<td>0.57</td>
<td>195</td>
<td>34.4%</td>
<td>0.17 [0.06, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Dijkhuizen 2008</td>
<td>-1.49</td>
<td>0.88</td>
<td>614</td>
<td>-1.56</td>
<td>0.9</td>
<td>625</td>
<td>40.7%</td>
<td>0.07 [-0.03, 0.17]</td>
<td></td>
</tr>
<tr>
<td>Hamadani 2001</td>
<td>-1.2</td>
<td>0.6</td>
<td>97</td>
<td>-1.3</td>
<td>0.8</td>
<td>101</td>
<td>10.4%</td>
<td>0.10 [-0.10, 0.30]</td>
<td></td>
</tr>
<tr>
<td>Hershkovitz 1999</td>
<td>-0.64</td>
<td>0.88</td>
<td>14</td>
<td>-1.02</td>
<td>1.09</td>
<td>11</td>
<td>0.6%</td>
<td>0.38 [-0.41, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Wasantwisut 2006</td>
<td>-0.7</td>
<td>0.8</td>
<td>151</td>
<td>-0.7</td>
<td>0.7</td>
<td>153</td>
<td>14.0%</td>
<td>0.00 [-0.17, 0.17]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>1067</td>
<td></td>
<td></td>
<td>1085</td>
<td>100.0%</td>
<td>0.10 [0.04, 0.16]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.79$, df = 4 ($P = 0.43$); $I^2 = 0$

Test for overall effect: $Z = 3.09$ ($P = 0.002$)

**Figure 5** Zinc Supplementation vs. Placebo: IQ score at 9 years of age

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pongcharoen 2011</td>
<td>92.9</td>
<td>12.3</td>
<td>139</td>
<td>93.5</td>
<td>11.7</td>
<td>139</td>
<td>100.0%</td>
<td>-0.60 [-3.42, 2.22]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>139</td>
<td></td>
<td></td>
<td>139</td>
<td>100.0%</td>
<td>-0.60 [-3.42, 2.22]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: $Z = 0.42$ ($P = 0.68$)

**Figure 6** Low Phytate vs. High Phytate Diet: Fecal zinc (mcg/kg/d)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy 2010</td>
<td>85.5</td>
<td>12.9</td>
<td>10</td>
<td>85.1</td>
<td>23.7</td>
<td>10</td>
<td>100.0%</td>
<td>0.40 [-16.32, 17.12]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td>10</td>
<td>100.0%</td>
<td>0.40 [-16.32, 17.12]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: $Z = 0.05$ ($P = 0.96$)

**Figure 7** Low Phytate vs. High Phytate Diet: Plasma zinc micromole/L

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
### Study or Subgroup

<table>
<thead>
<tr>
<th>Low Phytate</th>
<th>Mean (SD)</th>
<th>Total</th>
<th>High Phytate</th>
<th>Mean (SD)</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Test for overall effect: Z = 0.43 (P = 0.66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy 2010</td>
<td>10.3 (1.3)</td>
<td>10</td>
<td>9.8 (3.4)</td>
<td>10</td>
<td>10</td>
<td>100.0%</td>
<td>0.50 [-1.76, 2.76]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10</td>
<td>10</td>
<td>100.0%</td>
<td>0.50 [-1.76, 2.76]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 8

Zinc supplement v. Placebo: Wart remained at 2 months

### Study or Subgroup

<table>
<thead>
<tr>
<th>Zinc</th>
<th>Placebo</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Gurairi 2002</td>
<td>3 (23)</td>
<td>20</td>
<td>100.0%</td>
<td>0.00 [0.00, 0.09]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>23</td>
<td>20</td>
<td>100.0%</td>
<td>0.00 [0.00, 0.09]</td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>20</td>
<td>100.0%</td>
<td>0.00 [0.00, 0.09]</td>
</tr>
</tbody>
</table>

### Figure 9

Absorption of Zn from various salts in tortilla, outcome: 6.1 Serum Zinc.
Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

### 6.1.1 ZnO2 vs. ZnSO4

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtz 2005</td>
<td>10.3</td>
<td>1</td>
<td>7</td>
<td>10.3</td>
<td>1.2</td>
<td>13</td>
<td>0.00 [-0.99, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7</td>
<td></td>
<td>13</td>
<td>32.4%</td>
<td></td>
<td></td>
<td>0.00 [-0.99, 0.99]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

### 6.1.2 ZnO vs. ZnO+Na2EDTA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtz 2005</td>
<td>10.3</td>
<td>1</td>
<td>7</td>
<td>10.2</td>
<td>1.2</td>
<td>10</td>
<td>0.10 [-0.95, 1.15]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7</td>
<td></td>
<td>10</td>
<td>28.6%</td>
<td></td>
<td></td>
<td>0.10 [-0.95, 1.15]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 0.19 (P = 0.85)

### 6.1.3 ZnO vs. Na2ZnEDTA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtz 2005</td>
<td>10.3</td>
<td>1</td>
<td>7</td>
<td>10.8</td>
<td>0.9</td>
<td>12</td>
<td>-0.50 [-1.40, 0.40]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7</td>
<td></td>
<td>12</td>
<td>39.0%</td>
<td></td>
<td></td>
<td>-0.50 [-1.40, 0.40]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 1.09 (P = 0.28)

Total (95% CI) 21

Heterogeneity: Chi² = 0.89, df = 2 (P = 0.64); I² = 0%

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Chi² = 0.89, df = 2 (P = 0.64), I² = 0%

### Figure 10 Zinc Oxide High pH v ZnAcet Low pH, outcome: Urinary zinc.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc Oxide/high pH Mean</th>
<th>SD</th>
<th>Total</th>
<th>Zinc Acetate/low pH Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson 1995</td>
<td>0.422</td>
<td>0.209</td>
<td>8</td>
<td>0.649</td>
<td>0.233</td>
<td>8</td>
<td>-0.23 [-0.44, -0.01]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 8

Heterogeneity: Not applicable

Test for overall effect: Z = 2.05 (P = 0.04)

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

**Figure 11.** Zinc Oxide High pH v ZnAcet Low pH, outcome: Plasma zinc.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc Oxide/high pH Mean</th>
<th>SD</th>
<th>Total</th>
<th>Zinc Acetate/low pH Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson 1995</td>
<td>66</td>
<td>3.5</td>
<td>10</td>
<td>524</td>
<td>112</td>
<td>10</td>
<td>100.0%</td>
<td>-458.00 [-527.45, -388.55]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>-458.00 [-527.45, -388.55]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 12.93 (P < 0.00001)

**Figure 12** Absorption of Zn from various salts in tortilla, outcome: Serum Zinc

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1.1 ZnO₂ vs. ZnSO₄</td>
<td>10.3</td>
<td>1</td>
<td>7</td>
<td>10.3</td>
<td>1.2</td>
<td>13</td>
<td>32.4%</td>
<td>0.00 [-0.99, 0.99]</td>
</tr>
<tr>
<td>Holtz 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7</td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
<td>32.4%</td>
<td>0.00 [-0.99, 0.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

| 6.1.2 ZnO vs. ZnO+Na₂EDTA | 10.3 | 1   | 7     | 10.2         | 1.2| 10    | 28.6%  | 0.10 [-0.95, 1.15]               |
| Holtz 2005             |      |     |       |              |    |       |        |                                  |
| Subtotal (95% CI)      | 7     |     |       | 10           |    |       | 28.6%  | 0.10 [-0.95, 1.15]               |

Heterogeneity: Not applicable

Test for overall effect: Z = 0.19 (P = 0.85)

| 6.1.3 ZnO vs. Na₂ZnEDTA | 10.3 | 1   | 7     | 10.8         | 0.9| 12    | 39.0%  | -0.50 [-1.40, 0.40]              |
| Holtz 2005             |      |     |       |              |    |       |        |                                  |
| Subtotal (95% CI)      | 7     |     |       | 12           |    |       | 39.0%  | -0.50 [-1.40, 0.40]              |

Heterogeneity: Not applicable

Test for overall effect: Z = 1.09 (P = 0.28)

| Total (95% CI)        | 21    |     | 35    | 100.0%     |     |       | -0.17 [-0.73, 0.40]               |
| Heterogeneity: Chi² = 0.89, df = 2 (P = 0.64); I² = 0% |

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Chi² = 0.89, df = 2 (P = 0.64), I² = 0%

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
**Figure 13.** Zinc v Placebo, outcome: Wart remained at 1 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Al-Gurairi 2002</td>
<td>9</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>20</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: \( Z = 2.61 \) (\( P = 0.009 \))

**Figure 14.** Zinc v Placebo, outcome: Pain episodes in SCD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bao 2008</td>
<td>1</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Prasad 1999</td>
<td>7</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>29</td>
<td>28</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>11</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.05, df = 1 (\( P = 0.81 \)); I² = 0%
Test for overall effect: \( Z = 1.30 \) (\( P = 0.19 \))

**Figure 15.** Zinc v Placebo, outcome: Number of infections in SCD

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bao 2008</td>
<td>Events 1, Total 18</td>
<td>Events 9, Total 18</td>
<td>Weight 100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>Events 18, Total 18</td>
<td>Events 18, Total 18</td>
<td>Weight 100.0%</td>
</tr>
</tbody>
</table>

**Heterogeneity:** Not applicable

**Test for overall effect:** $Z = 2.50$ ($P = 0.01$)

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

**Zinc Absorption Critically Appraised Topic (CAT)**

This synthesis includes 19 papers and other resources that are not amenable to be analyzed with RevMan or GradePro.

### Synthesis of relevant studies:

<table>
<thead>
<tr>
<th>Author, date, country, and industry of funding</th>
<th>Patient Group</th>
<th>Research Design</th>
<th>Treatments &amp; Outcomes</th>
<th>Significant results</th>
<th>Notes &amp; Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International and U. S. Government Documents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Benoist, B., Darnton-Hill, I, Davidsson, L., Fonatin, O., &amp; Hotz, C. (2007), Conclusions of the Joint WHO/UNICEF/IZiNCG interagency meeting on zinc status indicators. <em>Food and Nutrition Bulletin</em>, 28, 3(supplement) S480-S487.</td>
<td>Children and adults</td>
<td>Narrative summary of a meeting.</td>
<td>N/S</td>
<td>Three categories of population indicators considered were biochemical, dietary and functional Biochemical: serum or plasma zinc best for population risk of zinc deficiency. Inadequate for individuals because blood levels are affected by recent meals, time of day, age, sex, presence of systemic infection or inflammation. They recommend cutoffs based on age, sex, time of day Dietary: useful for assessing risk for zinc deficiency in a population. Useful and should be used in conjunction with biochemical measures. The Estimated Average Requirement (EAR) should be used for determining dietary adequacy. “Risk of zinc deficiency is considered to be elevated and a public health concern when prevalence or probability of inadequate intake is &gt; 25% of the population. Functional: Height of length for age—although not specific for Zn deficiency and can only be used in children. Need to know the exact age of the child. For population assessment children under 5 years who are &gt; -2SD below the age specific median of the reference population.</td>
<td></td>
</tr>
</tbody>
</table>

| **MetaAnalyses that cannot be entered into GradePro** |               |                |                        |                    |                    |
| Dekker, L. H., & Villamor, E. (2010). | 21 RCTs including | Meta-analysis | Treatment: Doses ranged 10- | Hemoglobin concentration: 2 studies were determined to be outliers, since their Well done MA, did not report all data necessary to enter | |

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu 53
### Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

**Zinc supplementation in children is not associated with decreases in hemoglobin concentrations.**

*Journal of Nutrition, 140, 5, 1035-1041.*

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

---


Effects of micronutrients on growth of children under 5 y of age: Meta-analysis of single and multiple nutrient interventions.


56 RCTs on children < 5 years old. Median duration of studies was 8-64 weeks, Number of subjects included was 11,547.

**Meta analysis**

### Treatment of Disease


299 children aged 2-23 months in South India.

**RCT**

### Treatment: Treatment group:

10 mg zinc sulfate tablets twice daily

Control: 10 mg placebo tablet twice daily.

Both group received standard treatment for severe pneumonia

### Outcomes:

Time to resolution of these three symptoms:

1) Outcome one- not significantly different

Zinc- 82.2 (68.1, 87.3)

Control- 75.9 (71.2, 88.0)

RR 0.93 (0.74,1.17) p=0.722

2) Outcome two- not significantly different

Zinc- 87.2 (70.7,95.2) Control- 76.2 (72.3,88.1)

RR 0.93 (0.72,1.21) p=0.589

3) Outcome three- not significantly different

Zinc- 111.3 (88.5, 138.0)

Control- 96.7 (78.2, 112.9)

RR 0.86 (0.62,1.18) p=0.353

### Time to resolution

Duration of hospitalization (hours)

Zinc- 71.1 (68.1, 87.3)

Notes:

Each subject received 2 tablets twice on day 1, and one table, twice daily thereafter.

Tablets were dissolved in 1 tsp distilled water for young infants.

Limitations:

Analyzed by intention to treat analysis. 3 subjects withdrew, one in the treatment group and two in the control group. State ITT, but one subject in the zinc group was excluded from the analysis.

Well done MA, did not report all data necessary to enter into GradePro.

Different from the results by Brown et al. Authors postulate The inclusion of more recent studies not included in Brown may be a factor Prevalence of stunting in the recent studies may be lower Decrease in publication bias, more studies with negative results may be published.

---

"Confirm there is no consistent evidence for an adverse effect of zinc supplementation on hemoglobin among apparently healthy children."

Duration of treatment 4-15 months.

20 mg/d of zinc

Outcome:

Hemoglobin conc

effect sizes were 3-5 times as large as the next largest effect size.

With the excluded studies effect size was 0.8 g/L (95%CI: -0.6,202; p=0.27)

Without the excluded studies the effect size was -0.2 g/L (95% CI: -0.9, 0.5 p=0.59).


Effects of micronutrients on growth of children under 5 y of age: Meta-analysis of single and multiple nutrient interventions.


56 RCTs on children < 5 years old.

Median duration of studies was 8-64 weeks, Number of subjects included was 11,547.

Meta analysis

**Treatment:**

Zinc supplementation doses ranged from 20 mg/week to 20 mg/d.

Outcomes:

Length (height) for age

Weight gain

Weight for length z score.

Using the WHO growth standards.

Length for age- thirty studies had a positive effect, and 11 were statistically significant. However the weighted mean effect was small and not significant. (0.07; 95% CI: - 0.03, 0.17).

Weight gain: 33 studies had a positive effect, and 10 were statistically significant. The overall weighted mean effect was 0.09 (95% CI: -0.11,0.25)

Weight for length z score- 22 studies (33 data sets) weighted mean effect size was 0.06 (95% CI; 0.006, 0.11).

Well done MA, did not report all data necessary to enter into GradePro.

Different from the results by Brown et al. Authors postulate The inclusion of more recent studies not included in Brown may be a factor Prevalence of stunting in the recent studies may be lower Decrease in publication bias, more studies with negative results may be published.
### Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

**India**

**Pneumonia**

1. RR > 50 bpm and SaO2 < 93%
2. Outcome one AND inability to drink
3. Outcome one AND chest in-drawing

Duration of hospitalization
Plasma zinc level at discharge.

<table>
<thead>
<tr>
<th>Outcome one</th>
<th>AND chest in-drawing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control- 72.3 (67.7,79.6) RR- 0.93 (0.74-1.17) p=0.550</td>
<td></td>
</tr>
</tbody>
</table>

Discharge serum zinc
Zinc- 13.0±2.5 mM/L
Control-12.0±4.1 mM/L
P=0.013


<table>
<thead>
<tr>
<th>Case control</th>
<th>Serum zinc levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc (mcg/dl)</td>
<td>Ferritin</td>
</tr>
<tr>
<td>β-thalassemia</td>
<td>108.17 +17.72 DNR</td>
</tr>
<tr>
<td>Control</td>
<td>93.48 +13.62 DNR</td>
</tr>
</tbody>
</table>

Excluded if on hydroxyl urea or zinc dietary supplement in the last year.
Collected Demographic and anthropometric data, time of diagnosis, initiating time of blood transfusion, as well as chelation therapy, daily dose of desferrioxamine as iron), patient’s compliance toward desferrioxamine, time interval between blood transfusions, history of splenectomy, and patient medications
They did not report ferritin levels

### Absorption


<table>
<thead>
<tr>
<th>10 healthy subjects (5 males)</th>
<th>2 way 4 phase crossover study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments:</td>
<td></td>
</tr>
<tr>
<td>High pH (&gt; 5)</td>
<td></td>
</tr>
<tr>
<td>Low pH (≤3)</td>
<td></td>
</tr>
<tr>
<td>Zinc acetate</td>
<td>524±112</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>364±152</td>
</tr>
<tr>
<td>Single oral zinc equivalent to 50 mg of elemental zinc.</td>
<td>378±126</td>
</tr>
<tr>
<td>Outcomes:</td>
<td></td>
</tr>
</tbody>
</table>

Plasma zinc

Authors suggest taking zinc away from taking pH altering medicines.
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>821 children aged 12-16 years. HGB &gt; 80 g/L. Zinc and iron deficiency is prevalent in this region this study was carried out.</td>
</tr>
</tbody>
</table>

| Jalla, S., Krebs, N. F., Rodden, D., & Hambidge, K. M. (2004). Zinc homeostasis in premature infants. Healthy adults N= 109 (21-51 years) 4 week dietary | Cross over design. Goal was to use data generated to create | Treatments 4 week equilibration to experimental diet a. High zinc | Lower zinc intake resulted in higher fractional zinc absorption. Higher zinc increased the amount of zinc absorbed |

---

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
**Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc**

<table>
<thead>
<tr>
<th>Minnesota</th>
<th>zinc equilibration 8 week dietary zinc equilibration</th>
<th>Subjects consumed 4-29 mg Zn/d with five molar ratios of phytate to zinc from 2 to 7 AND 5 molar ratios from 15 to 23</th>
<th>predictive models of zinc absorption with varying zinc and phytate concentrations</th>
<th>a. All zinc level diets</th>
<th>The bioavailability of zinc appears to be more important than the amount of zinc in the diet. Fraction absorption is more dependent on phytate concentration than zinc concentration.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado</td>
<td>6 normal males from 27-44 years of age with possible zinc deficiency.</td>
<td>Cohort</td>
<td>Treatment: First test: 200 mg of zinc sulfate was administered in a fasting state. Second test: 200 mg of zinc sulfate was administered with a light meal (4 slices whole grain bread with butter and cheese, 1 glass of milk)</td>
<td>Outcomes: Serum zinc at 0.5, 1, 2 4 and 6 hours.</td>
<td>In the fasting group, serum zinc levels rose after ingestion of supplemental zinc. At 2 hours post ingestion, s. zinc was 159% higher than fasting zinc level. In the group that ingested a light meal along with supplemental zinc, s. zinc levels remained lower than fasting levels for 6 hours after ingestion of the supplement. Notably, s. zinc was 13% below fasting level at 1 hour and 8% below fasting at 2 hours.</td>
</tr>
<tr>
<td>Keyzer, J.J., Oosting, E., Wolthers, B. G., &amp; Muskiet, F. A. J. (1983). Zinc absorption after oral administration of zinc sulfate. <em>Pharmaceutisch Weekblaan Scientific Edition, 5</em>, 252-253.</td>
<td>14 infants (8 male) Mean gestational age of 31</td>
<td>Cohort</td>
<td>Treatment: Treatment 1 Mother’s own milk fortified with human milk</td>
<td>They state” There was no significant difference of any variable between the preterm formula and fortified human milk; outcomes included are dietary zinc, fraction absorption of zinc, total absorbed</td>
<td>Nestle Nutrition sponsored a researcher, no role of Nestle employees stated in the paper. Low risk for bias. In reporting the outcomes, the...</td>
</tr>
</tbody>
</table>
### Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<table>
<thead>
<tr>
<th>Researcher(s)</th>
<th>Study Design</th>
<th>Duration</th>
<th>Appropriate for Gestational Age</th>
<th>Recruitment Period</th>
<th>Fortifier</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Data Table</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKenna, A. A., Ilich, J. Z., Andon, M. B., Wang, C., &amp; Matkovic, V. (1997).</td>
<td>26 adolescent females during a 14 day period</td>
<td>Crossover study</td>
<td>Consumed a metabolic diet containing 722 mg Ca and 6.3 mg Zn.</td>
<td></td>
<td>Treatment: Group 1- 1000 mg supplemental Ca/d as citrate malate salt. Group 2: placebo.</td>
<td>There was no difference in the components of zinc metabolism when 1000 mg of Ca in the form of calcium-citrate-malate was supplemented. Components of zinc metabolism include zinc intake, fecal excretion of zinc, urinary excretion of zinc, zinc balance, net absorption of zinc and zinc absorption (% of intake).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nève, J., Hanocq, M., Peretz, A., Khalil, F. A., &amp; Pelen, F. (1991).</td>
<td>10 subjects</td>
<td>Crossover</td>
<td>45 mg of zinc as zinc gluconate (Rubozinc®) administered under 3 conditions Condition 1: after an overnight fast Condition 2: during a standardized breakfast and Condition 3: 2 hours after this meal.</td>
<td></td>
<td>Treatment:</td>
<td>Taking zinc with a meal increases the time for the appearance of the ingested zinc to be detectable in the serum. Taking zinc with a meal also reduced the maximum serum zinc level obtainable and the total zinc absorbed. Zinc absorption rate, maximum concentration and area under curve (AUC) was not different when zinc taken fasting was compared to zinc taken 2 hours after a meal.</td>
<td></td>
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</tr>
</tbody>
</table>

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If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu
## Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oksel, F., Köksyo, H., Taneli, B. (1996). Zinc tolerance test patterns in normal children and in moderate and severe zinc deficiency states. Indian Journal of Pediatrics, 63, 655-658.</td>
<td>60 Guatemalan school children Age 7.5-12 years</td>
<td>Cross-sectional cohort study</td>
<td>Did not find significant difference in growth velocity with the reduction of dietary phytate, addition of zinc supplement (5 mg/d) nor with the combination of reducing phytate and adding zinc.</td>
<td>The authors opine that since maize makes up a small proportion of complimentary foods in this group difference was not seen.</td>
</tr>
<tr>
<td>Spencer, H., Rubio, N., Kramer, L., Norris, C., &amp; Osis, D. (1987). Effect of zinc supplements on the intestinal absorption of calcium. Journal of</td>
<td>15 adult males in a metabolic research ward 2 subjects had renal failure, one mild</td>
<td>Cohort, crossover design</td>
<td>High zinc intake decreased Ca absorption at low Ca intake, but not at normal Ca intake. When zinc supplement was added, Ca⁴⁷ (calcium marker) decreased and fecal Ca increased. Same effect was seen with zinc sulfate and with zinc gluconate.</td>
<td>What they call a study is really one patient completing that section of the crossover design investigation. When using high doses of supplemental zinc, should assure patient is on at least DRI for calcium.</td>
</tr>
</tbody>
</table>

Serum zinc at -0.50, -0.25, 0.00 (ingestion of zinc supplement), 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, and then every 0.5 hour until 8 hours after zinc ingestion.

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### Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

**the American College of Nutrition, 6, 1. 47-51.**

<table>
<thead>
<tr>
<th>(BUN= 48 &amp; Creat =4.0 mg%) and one chronic stable (BUN = 26 &amp; Creat = 26 mg%) No other medications</th>
<th>normal calcium diet (800 mg/d) Also re-did the same study in two subject but used zinc gluconate.</th>
</tr>
</thead>
</table>


**Australia**

<table>
<thead>
<tr>
<th>Children with celiac disease (CD) (Marsh score ≥ 3 use as diagnostic criteria) n=16 were compared to children without CD n= 22. Age of children recruited was 2-18 years. Quasi-experimental the CD cohort was compared to the not CD cohort.</th>
<th>Zinc absorption Exchangeable zinc pool No significant difference in fractional zinc absorption between children with CD than those without CD. There was a significant difference in the exchangeable zinc pool between children with CD and those without CD. Children with CD had an exchangeable zinc pool that was 32% smaller.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Zinc dose</th>
<th>FAZ</th>
<th>AZ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>0.73 ±0.18</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>5 mg</td>
<td>0.68 ±0.25</td>
<td>3.5 ± 1.3</td>
</tr>
<tr>
<td>10 mg</td>
<td>0.71 ± 0.11</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>15 mg</td>
<td>0.62 ± 0.14</td>
<td>9.5 ± 2.2</td>
</tr>
<tr>
<td>20 mg</td>
<td>0.54 ± 0.2</td>
<td>11.0 ± 2.2</td>
</tr>
<tr>
<td>30 mg</td>
<td>0.37 ± 0.07</td>
<td>11.2 ± 2.1</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>8 healthy adults (3 men and 5 women) Age 33.8 ± 9.8 years Crossover study Zinc administered as 6 different concentrations in three phases. There was a three week washout period</th>
<th>Treatment: Phase 1: 2 and 5 mg of aqueous Zn Phase 2: 10 and 15 mg of aqueous Zn Phase 3: 20 and 30 mg of aqueous Zn Outcomes: Fractional</th>
</tr>
</thead>
</table>

FAZ= fractional absorption of zinc
AZ = absorbed zinc
Using regression analysis, 13 mg of zinc as aqueous zinc sulfate is an estimate of the maximum amount of zinc that will be absorbed, regardless of the amount of zinc ingested. Increments in absorbed zinc were progressively smaller as the size of the dose increased.

Population of this study is healthy adults
Zinc absorption from aqueous solution is different than zinc from foods. No data for tablets or capsules.

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### Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<table>
<thead>
<tr>
<th>1573.</th>
<th>Australia between phases.</th>
<th>absorbed zinc Absorbed zinc</th>
</tr>
</thead>
</table>

**Growth**


Japan

21 children prepubertal, (11 male) short, without endocrine abnormality
Mild to moderate zinc deficiency by zinc kinetics studies

Group 1: n= 10, (5 boys) 5 mg/kg zinc sulfate orally for 6 months
Group 2: n= 11 (6 boys) control
Outcomes
Weight Height Zinc clearance Serum zinc

Report linear growth velocity, calorie intake serum levels of zinc, calcium, phosphorus, and alkaline phosphatase, the percentage of tubular re-absorption of phosphorus TmP/GFR ration and serum level of osteocalcin and plasma level of IGF-1 were all improved at least P< 0.05

220 screened, 11 selected
- Height for age < 2 SD
- Apparently good health
- S. growth hormone > 10 ng/ml insulin
- Zinc clearance > 20 ml/kg per hour
- Pre-pubertal status throughout the study (Tanner staging)

### Epidermolysis Bullosa


Children with dystrophic EB

Cohort

Treatment
All were treated with diet instruction,
All were supplemented with fortified cow milk supplement,
Sustained release zinc sulfate for those with low plasma zinc or dietary intakes < 10 mg/d (22 mg

Initial plasma zinc was low in 5 of 13 subjects and serum albumin was low in 5 of 14 subjects. Many were already on supplemental zinc and total zinc intake was not correlated to zinc level.
Parents described sporadic administration of zinc d/t difficulties giving the supplement
Recommend alternating iron and zinc due to competition, however, other studies have shown otherwise. (See Dekker, 2010)

Difficult to assess if outcomes were truly assessed.
Many biases, poor design.

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## Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

### Elemental Zinc

Sodium iron edetate elixir for those with had increase TIBC, low serum iron or dietary intake <10mg/d. Vitamins when dietary intake was poor.

### Outcomes

- Anthropometrics
- Dietary intake

### Treatment

None

### Outcomes

Blood levels of the following nutrients:

- Vitamins A, C, B12, B6 and thiamine,
- riboflavin and folate,
- Minerals zinc, copper and iron.

#### EB Simplex (2/43), Junctional (1/10) and Dominant Dystrophic (1/6) were zinc deficient.

(erythrocyte zinc)

#### Imprecise. Low number of cases with low zinc levels.

### Eczema

- Types:
  - Simplex- 48
  - Junctional-10
  - Recessive dystrophic-9
  - Dominant dystrophic- 6

#### Treatment

None

#### Outcomes

Blood levels of the following nutrients:

- Vitamins A, C, B12, B6 and thiamine,
- riboflavin and folate,
- Minerals zinc, copper and iron.

**EB simplex (2/43), junctional (1/10) and dominant dystrophic (1/6) were zinc deficient.**

<table>
<thead>
<tr>
<th>Types</th>
<th>Subjects with EB</th>
<th>Cross-sectional laboratory survey</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>EB simplex (2/43), junctional (1/10) and dominant dystrophic (1/6) were zinc deficient. (erythrocyte zinc)</th>
<th>Imprecise. Low number of cases with low zinc levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplex</td>
<td>48</td>
<td></td>
<td>None</td>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junctional</td>
<td>10</td>
<td></td>
<td>None</td>
<td>levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recessive dystrophic</td>
<td>9</td>
<td></td>
<td>None</td>
<td>of the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant dystrophic</td>
<td>6</td>
<td></td>
<td>None</td>
<td>following</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrients</td>
<td></td>
<td></td>
<td>vitamins</td>
<td>nutrients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A, C, B12, B6 and thiamine, riboflavin and folate, Minerals zinc, copper and iron.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Contamination


#### Treatment

None

#### Outcomes

Plasma and leukocyte conc. of zinc copper and selenium.

**There was no difference in plasma or leukocyte zinc between subjects with eczema and controls**

<table>
<thead>
<tr>
<th>Types</th>
<th>Subjects with EB</th>
<th>Cross-sectional laboratory survey</th>
<th>Treatment</th>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>23</td>
<td></td>
<td>None</td>
<td>Blood levels of the following nutrients:</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>24</td>
<td></td>
<td>None</td>
<td>vitamins A, C, B12, B6 and thiamine, riboflavin and folate, Minerals zinc, copper and iron.</td>
<td></td>
</tr>
<tr>
<td>Adults 18-82 years.</td>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Contamination


#### Treatment

Bench study 7 zinc supplements were analyzed for zinc (Zn) and

See Table 1. (Below)

Krone postulated Cd exposure in childhood via Zn supplementation may be a factor in early occurrence of renal dysfunction in the future. Efforts should be made to identify the sources and more strictly control the

<table>
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<tr>
<th>Types</th>
<th>Subjects with EB</th>
<th>Cross-sectional laboratory survey</th>
<th>Treatment</th>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td></td>
<td>Bench study 7 zinc supplements were analyzed for zinc (Zn) and</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Contamination

- The FDA Total Diet Study suggests that the mean lifetime exposure to total Cd from all food (excluding shellfish) is 10 µg/person/day.
Table 1. Zinc and Cadmium content of various zinc supplements.

<table>
<thead>
<tr>
<th>Salt form (single or multi supplement)</th>
<th>Stated Zn/Tablet (mg)</th>
<th>Measured Zn/Tablet (mg)</th>
<th>Measured Cadmium/Tablet µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Zinc gluconate (single)</td>
<td>50</td>
<td>50.3</td>
<td>0.18</td>
</tr>
<tr>
<td>2 Zinc gluconate (single)</td>
<td>60</td>
<td>62.2</td>
<td>0.19</td>
</tr>
<tr>
<td>3 Zinc citrate, chelate, picolinate (multi)</td>
<td>50</td>
<td>50.8</td>
<td>0.19</td>
</tr>
<tr>
<td>4 Zinc chelate (multi)</td>
<td>50</td>
<td>31.0</td>
<td>2.0</td>
</tr>
<tr>
<td>5* Zinc – not stated</td>
<td>50</td>
<td>71.0</td>
<td>3.6</td>
</tr>
<tr>
<td>6 Zinc sulfate (multi)</td>
<td>7.5</td>
<td>9.79</td>
<td>0.95</td>
</tr>
<tr>
<td>7 Zinc gluconate (single)</td>
<td>50</td>
<td>54.3</td>
<td>1.14</td>
</tr>
</tbody>
</table>

*experimental formulation, not available to the public.

Cadmium facts:
- Tolerable Daily Intake (TDI) = 55µg/day
- Absorbed Cd is eliminated slowly, Biological half life is ~ 38 years
- Deposited in the kidneys
- Long term exposure with an accumulation of Cd levels 180-220 µg/g tissue kidney dysfunction can occur