From A to Zinc: the evolving concept of micronutrient supplementation

Does one size fit all? Modulation of antioxidant supplementation in the ICU

M. Berger (CH)
FROM A TO ZINC: THE EVOLVING CONCEPT OF MICRONUTRIENT SUPPLEMENTATION

DOES ONE SIZE FIT ALL?

MODULATION OF ANTIOXIDANT SUPPLEMENTATION IN THE ICU

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Disclosure

Grants: Aguettant, Baxter, BBraun, Fresenius Kabi

Lecturer: Baxter, BBraun, Fresenius Kabi, Nestlé-Novartis

Advisory board: Baxter, Fresenius Kabi, Aguettant

Bonds ...: none
One size?

Many characteristics differ

- Metabolism (age, sex)
- Preadmission status
- Morphology (BMI)
- Nutrient composition (balanced?)
- Nutrient delivery? Under- Over-feeding?
- Disease impact on status (losses..)
- Disease related oxidative stress
- Disease duration
Growth percentiles

Girls 0-36 months

Boys 0-36 months

Table 1  Suggested paediatric parenteral trace element provision

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Zinc μg/kg/day [8]</th>
<th>Copper μg/kg/day [28]</th>
<th>Chromium μg/kg/day [8,26]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm infant &lt;3 kg</td>
<td>400</td>
<td>20</td>
<td>0.05–0.2</td>
</tr>
<tr>
<td>Term infant 3–10kg</td>
<td>250</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>Child 10–40kg</td>
<td>50</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>Adolescent &gt;40kg</td>
<td>2000–5000</td>
<td>200–500</td>
<td>5–15</td>
</tr>
<tr>
<td>Adult</td>
<td>2500–5000</td>
<td>300–500</td>
<td>10–15</td>
</tr>
</tbody>
</table>

Recomended for 75 kg:
- Cu: 1.5 mg 1.0-1.2
- Fe: 3.75 mg 1-2
- Se: 140 μg 60
- Zn: 18.75 mg 5-7
Lean, BMI: < 20
Normal BMI: 20-25

Overweight BMI: 25-30

Obese BMI: > 30

Anamnestic Body Weight before ICU admission

Ideal Body Weight according to body height and sex

FIRST 24-48 Hours after ICU admission
20 Kcal/kg body weight/d

48 Hours after ICU admission
25-30 Kcal/kg body weight/d
The argument for \( \uparrow \) selenium intake


Recent mean levels of serum or plasma Se in Europe compared with (--), bottom tertile in Nutritional Prevention of Cancer (NPC) trial of Clark et al. (1996); (·····), level required for optimal plasma GPx activity
Plasma redox status relates to severity in critically ill patients


APACHE III scores and plasma redox status ($r^2 = 0.56; p < .001$) as defined by the ratio total antioxidant capacity (mM) / lipoperoxides (uM)

APACHE III scores and plasma myeloperoxidase concentrations ($r^2 = 0.58; p < .001$)

73 patients at admission to a mixed ICU: 8 deaths
Trace elements
Acute phase response
Shenkin, Nutrition 11:100, 1995

Incision

Time (hours)

µmol / L

0 5 10 15 20 25
-16 -8 0 8 16 24 32 40 48

Zn
Fe
Cu
Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients

*Forceville X et al, CCM 26:1536, 1998*

Admission plasma [Se] related to severity of sepsis

*Worsening with ↑ severity*
Replace or supplement?
2 distinct aims

Losses +++
Insufficient Intakes

Deficit +

Replacement +++

Toxicity?
Micronutrient losses during CVVH

Berger MM et al, Amer J Clin Nutr, 410, 2004

Plasma Cu, Se, Zn, and thiamine in effluents from patients with acute renal failure under CRRT with either Na-bicarbonate (Bic group; Full) or Na- lactate (Lac group; □)
Cu, Se & Zn balances after major trauma

Berger MM et al, J Trauma, 40:103, 1996

Copper

mg / 24h

Days

0 1 2 3 4 5 6 7

Zinc

mg / 24h

Days after injury

0 1 2 3 4 5 6 7

n = 11
x ± sd

Cu, Se & Zn balances after major trauma

Berger MM et al, J Trauma, 40:103, 1996

Copper

mg / 24h

Days

0 1 2 3 4 5 6 7

Zinc

mg / 24h

Days after injury

0 1 2 3 4 5 6 7

n = 11
x ± sd
Trace element and mineral losses in major burns


∑ Losses in 7 days:
Cu: 20-40% body content
Se: 10%
Zn: 10%

N=10, 33% BSA
Antioxidants in major burns
Accelerated MDA decay with trace elements
*Berger & Chiolero, Burns, 21: 507, 1995*

**Graph: MDA (µmol/24hr)**
- **Group C**
- **Group TE**

**Design:** PCT
- 11 patients (5 / 6)
- BSA 42 / 43 %
- Group control: ø
- Group TE: Cu, Se, Zn
- Urine: 24 hr coll.

**p < 0.03**

MDA = malondialdehyde
Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations\textsuperscript{1−3}

Mette M Berger, Malcolm Baines, Wassim Raffoul, Messod Benathan, René L Chiolero, Chris Reeves, Jean-Pierre Revelly, Marie-Christine Cayeux, Isabelle Sénéchaud, and Alan Shenkin

Mean plasma TE over time

- **Copper**: μmol/d
- **Zinc**: μmol/L
- **Selenium**: μ/L
- **plasma GSHPx**: U/L

Am J Clin Nutr 2007; 85: 1293
TE after major burns increase [burned skin] and modulate local protein metabolism

Trace element (Cu, Se, Zn) substitution in Burns – Reduction of nosocomial pneumonia


Aggregation of 2 consecutive Randomized Trials → IV
- Cu 3 mg
- Se 300 mcg
- Zn 30 mg

Log Rank p=0.0014
Wilcoxon p=0.0019

65% reduction of pneumonia risk

n = 41
Burns 46% BSA
AOX trial - 200 critically ill: trauma-cardiac-SAH
Se, Zn, Vit E, Vit C, Vit B1
Berger et al Crit Care 2008 12:R101

- 11 days
Antioxidant interactions
Berger & Chiolero, CCM, 2007, 35(suppl) S584
Selenium in ICU septic patients – PRCT
Angstwurm et al- CCM 35:118,2007

249 patients - severe sepsis or septic shock: 1000 mcg Se or placebo daily for 2 weeks after a loading dose
Kaplan-Meier survival curves in patients by intention to treat analysis. Difference between groups by log rank test.

The estimated mean survival time was 19.7 days in Se1 patients (bold line) versus 16.4 days in the Se0 group (dotted line) (p = 0.0476).
Micronutrient supplementation for critically ill adults: a systematic review and meta-analysis


Effect of micronutrient supplementation on overall mortality in critically ill patients
REDOXS: A randomized trial of high dose Glutamine and Antioxidants in critically ill patients with MOF
Heyland et al, NEJM 2013

Antioxidant vs. no- AOX

Kaplan-Meier 6 Month Survival curves

n=1218
Selenium – que passa?

- SIGNET: *a small signal in favor of Se*
- REDOXS: *no Se deficit*

![Graph showing selenium levels over days for AOX and No AOX groups with number of patients for each day: 31 for AOX on Day 1, 28 for AOX on Day 4, 25 for AOX on Day 7; 30 for No AOX on Day 1, 26 for No AOX on Day 4, 19 for No AOX on Day 7.](image-url)
<table>
<thead>
<tr>
<th>Weight</th>
<th>Addamel®N</th>
<th>Tracutil®</th>
<th>Decan®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tracitrans®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu</td>
<td>mg</td>
<td>1.27</td>
<td>0.76</td>
</tr>
<tr>
<td>Fe</td>
<td>mg</td>
<td>1.11</td>
<td>1.95</td>
</tr>
<tr>
<td>Se</td>
<td>µg</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Zn</td>
<td>mg</td>
<td>6.25</td>
<td>3.27</td>
</tr>
<tr>
<td>Mo</td>
<td>µg</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Mn</td>
<td>mg</td>
<td>0.27</td>
<td>0.55</td>
</tr>
<tr>
<td>Cr</td>
<td>µg</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Co</td>
<td>µg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>mg</td>
<td>0.95</td>
<td>0.57</td>
</tr>
<tr>
<td>I</td>
<td>µg</td>
<td>0.13</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Lab*  
Fresenius Kabi  
BBraun  
Aguettant
## Vitamin preparations compared to RDA

<table>
<thead>
<tr>
<th>Vitamines</th>
<th>RDA</th>
<th>Cernevit®</th>
<th>Soluvit®</th>
<th>Vitalipide®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit A (rétinol)</td>
<td>3300 UI</td>
<td>3500 UI</td>
<td>-</td>
<td>3300 UI</td>
</tr>
<tr>
<td>Vit D</td>
<td>400 UI</td>
<td>220 UI</td>
<td>-</td>
<td>200 UI</td>
</tr>
<tr>
<td>Vit E</td>
<td>10 UI</td>
<td>10,2 UI</td>
<td>-</td>
<td>10 UI</td>
</tr>
<tr>
<td>Vit K1</td>
<td>2,4 mg</td>
<td>-</td>
<td>-</td>
<td>0,15 mg</td>
</tr>
<tr>
<td>Vit B1 (thiamine)</td>
<td>3 mg</td>
<td>3,51 mg</td>
<td>3 mg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B2 (riboflavine)</td>
<td>3,6 mg</td>
<td>5, 67 mg</td>
<td>3,6 mg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B3 (PP, nicotinamide)</td>
<td>2,4 mg</td>
<td>40 mg</td>
<td>40 mg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B5 (pantothéniq)</td>
<td>5 à 10 mg</td>
<td>15 mg</td>
<td>16,5 mg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B6 (pyridoxine)</td>
<td>4 mg</td>
<td>4,53 mg</td>
<td>4 mg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B8 (biotine)</td>
<td>60 µg</td>
<td>60 µg</td>
<td>60 µg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B9 (ac. folique)</td>
<td>400 µg</td>
<td>414 µg</td>
<td>400 µg</td>
<td>-</td>
</tr>
<tr>
<td>Vit B12</td>
<td>5 µg</td>
<td>6 µg</td>
<td>5 µg</td>
<td>-</td>
</tr>
<tr>
<td>Vit C</td>
<td>100 mg</td>
<td>125 mg</td>
<td>100 mg</td>
<td>-</td>
</tr>
</tbody>
</table>

Too low for ICU
What about the Dose?

MEGA dose > 20 RDA

HIGH dose → 5-15 RDA

NUTRITIONAL dose → 2-3 RDA
Dose response curve

A+B+C deficiency, D suboptimal, E optimal, G toxicity, H lethal
Adjusted hazard ratios for all-cause mortality by serum selenium concentration in adult participants of the US 3rd National Health & Nutrition Examination Survey followed up for up to 18 years until the end of 2006. Shaded area: 95% CIs. Reference value (hazard ratio 1) set at the 10th percentile of the serum selenium distribution (105.8 μg/L) (Bleys et al 2008)

13 887 adult participants
Study participants were recruited from 1988 to 1994
One size – AOX micronut - Conclusion

**Nutrition IV micronutrients**
- 1 dose for all? Does not really make sense
- Children: adapted to weight & metabolic level
- ICU requirements ↑: no adapted product yet
  → monitoring is required for long stayers

**Replacement of losses**: required to restore normal AOX, immune and wound healing capacity

**Antioxidants**
- Requirements highly variable/ combinations?
- No single dose can be proposed

**High dose AOX > 15 * RDA ?**
- Not yet supported by evidence