Evidence for the Safety of Fortifying Flour with Iron in the Presence of Thalassemia and Other Blood Disorders

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The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention
Dietary Iron

- Essential micronutrient
- Most contained in red blood cells and recycled
- No mechanism for excretion
- Iron levels controlled by absorption
- Loss only through blood loss or sloughing
  - Normally lose 1 mg per day
  - Menstruation – 10 mg per cycle (more for heavy bleeders)
  - Blood Donation- 250mg
  - Increased demand due to pregnancy – 700mg
- Absorption is generally 5-10% of dietary intake
Iron Absorption and Transport

Secondary Iron Overload

- Iron absorption mediated by hepcidin
- Secondary iron overload caused by ineffective erythropoiesis
  - Hepcidin expression is decreased when erythropoiesis is increased
  - Due to downregulation of hepcidin
  - Failure to inhibit ferroportin
  - Increase iron export from enterocyte into plasma
- This is seen in “iron-loading anemias”

Some causes of secondary iron overload.

- **Hereditary disorders**
  - Thalassemia
  - Pyruvate kinase deficiency
  - Dyserythropoietic anemia
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Hereditary spherocytosis
  - Sideroblastic anemia (ALA-S deficiency)

- **Acquired disorders**
  - Sideroblastic and other dyserythropoietic anemias
  - Any anemia, except for that due to blood loss, in which multiple transfusions are required.

# Common Types of Alpha Thalassemia

<table>
<thead>
<tr>
<th># of Affected Genes (out of 4)</th>
<th>Alpha Thalassemia</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silent Carrier</td>
<td>No symptoms</td>
</tr>
<tr>
<td>2</td>
<td>$\alpha$ Thal trait</td>
<td>Microcytosis +/- Mild anemia</td>
</tr>
<tr>
<td>3</td>
<td>Hb H Disease</td>
<td>Moderate to severe anemia</td>
</tr>
<tr>
<td>4</td>
<td>$\alpha$ Thal Major (Hydrops Fetalis)</td>
<td>Usually die before or shortly after birth</td>
</tr>
</tbody>
</table>
## Common Types of Beta Thalassemia

<table>
<thead>
<tr>
<th># of Affected Genes (out of 2)</th>
<th>Beta Thalassemia</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>βThal trait/minor</td>
<td>Microcytosis, mild anemia</td>
</tr>
<tr>
<td>2</td>
<td>β Thal intermedia or β Thal Major (Cooley's Anemia)</td>
<td>TI - moderate anemia, not transfusion-dependent; TM - transfusion-dependent</td>
</tr>
</tbody>
</table>

- TI: Transfusion-Independent
- TM: Transfusion-Dependent
Thalassemia and Iron Overload

• **Complication**
  – Iron overload → organ damage

• **Mechanism for Development of Iron Overload**
  1. Blood transfusion
     • Blood transfusions (every 2-4 weeks for TM)
  2. Increased absorption of dietary iron due to ineffective erythropoiesis

• **Treatment**
  – Iron chelation therapy
     • Deferoxamine (standard therapy given overnight through a needle/pump under the skin)
     • Deferasirox (daily pill)
# Life Expectancy - Thalassemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regular transfusion</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>Regular transfusion + no chelation</td>
<td>10-15 years</td>
</tr>
<tr>
<td>Regular transfusions + desferrioxamine (DFO) chelation – Poor adherence</td>
<td>15-25 years</td>
</tr>
<tr>
<td>Regular transfusions + (DFO) chelation – Good adherence</td>
<td>At least 50 years</td>
</tr>
<tr>
<td>Regular transfusions + diverse chelation modalities [DFO, deferiprone (DFP), deferasirox (DFX), combination DFO and DFP] and improved monitoring of liver and myocardial iron content by magnetic resonance imaging</td>
<td>&gt; 50 years</td>
</tr>
</tbody>
</table>

Mechanisms of iron overload and which thalassemia patients are at risk

Transfused
- Thalassemia Major
  - When patients are transfused (e.g. b-thal major)
  - Accumulation is doubled compared to Thal intermedia

Non-transfused Thalassemia
- Thalassemia Intermedia
  - Rate of iron loading from the GI tract is 3-4 times greater than normal
  - Results in an increased iron burden between 2-5g per year
  - May need chelation as they get older
Mechanisms of iron overload and which thalassemia patients are at risk

Non-transfused

- Thalassemia Minor / Carriers
  - There are very few reports in the literature and studies present conflicting results
  - Evidence in total suggests that carriers are not at higher risk of iron-overload from dietary iron unless certain circumstances exist
    - Associated with coincidental HFE and other hemochromatosis causing gene mutations
    - Inappropriate therapy with very high levels of iron
Who Does Sickle Cell and Thalassemia Affect?

# Distribution of β-Thalassemia Carriers (CEE/CIS)

<table>
<thead>
<tr>
<th>Country</th>
<th>% with Thal Trait</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>8.4</td>
<td>Baghernajad-S L, 2009</td>
</tr>
<tr>
<td>Armenian</td>
<td>1-2</td>
<td>Kuliev AM, 1994</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>&gt;6 (0-20)</td>
<td>Kuliev AM, 1994</td>
</tr>
<tr>
<td>Bosnia</td>
<td>1.5</td>
<td>Efremov GD, 1992</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>2.5 (0.5-19.9)</td>
<td>Petkov GH 2007</td>
</tr>
<tr>
<td>Croatia (Dalmation Coast)</td>
<td>0.8 (6.9)</td>
<td>Efremov GD, 1992</td>
</tr>
<tr>
<td>Georgia</td>
<td>Up to 3</td>
<td>Kuliev AM, 1994</td>
</tr>
</tbody>
</table>
## Distribution of β-Thalassemia Carriers (CEE/CIS)

<table>
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<tr>
<th>Country</th>
<th>% with Thal Trait</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kosovo</td>
<td>2.0</td>
<td>Efremov GD, 1992</td>
</tr>
<tr>
<td>Macedonia</td>
<td>2.6 (1%-10%)</td>
<td>Efremov GD, 2007</td>
</tr>
<tr>
<td>Montenegro</td>
<td>1.9</td>
<td>Efremov GD, 1992</td>
</tr>
<tr>
<td>Romania</td>
<td>0.5%</td>
<td>Talmaci R, 2004</td>
</tr>
<tr>
<td>Serbia</td>
<td>1.8</td>
<td>Efremov GD, 1992</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>Estimated 10%</td>
<td>Baranov VS, 1993</td>
</tr>
<tr>
<td>Turkey (Adiyaman)</td>
<td>1.91</td>
<td>Genc A, 2012</td>
</tr>
<tr>
<td>Turkey (Konya)</td>
<td>2.0</td>
<td>Guler, E, 2007</td>
</tr>
<tr>
<td>Turkey</td>
<td>1.66 (1 -13)</td>
<td>Cavdar AO, 1971</td>
</tr>
<tr>
<td>Turkey</td>
<td>3.9</td>
<td>Koçak R, 1995</td>
</tr>
<tr>
<td>Turkmenistan</td>
<td>Estimated 10%</td>
<td>Baranov VS, 1993</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>Estimated 10%</td>
<td>Baranov VS, 1993</td>
</tr>
</tbody>
</table>
Births with Pathological Hemoglobin Disorders per 1,000 Live Births (CEE/CIS)

Map reformatted in: March of Dimes Global Report on Birth Defects – The Hidden Toll of Dying and Disabled Children
Conclusions

- Among those with thalassemia, evidence suggests that only thalassemia major and intermedia are at risk of secondary iron overload.
- Prevalence of clinically significant (Major and Intermedia) thalassemia is low in CEE/CIS.
- Early identification and appropriate clinical management should address risk of iron overload in persons with thalassemia major and intermedia.
Potential Recommendations

- In populations with a high prevalence of thalassemias and thalassemia traits
  - Early identification (screening for hemoglobinopathies) to identify persons with thalassemia major and intermedia
  - Regular monitoring of individuals for iron overload throughout lifespan if they have thalassemia
  - Education of patients thalassemia major and intermedia to avoid iron containing supplements and iron-rich foods
  - Population monitoring (public health surveillance) for iron deficiency AND for possible iron overload to assess effect of any program
Thank You

For more information please contact Centers for Disease Control and Prevention

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Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov   Web: www.cdc.gov

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