Iron overload in thalassemia major and sickle cell disease

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Brussels, Belgium

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DISCLOSURES

- None
THIS TALK IS APPLICABLE FOR:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia’s</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Membrane disorders (e.g. sferocytosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzym defects (e.g. PKD, G6PD)</td>
<td></td>
<td></td>
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<tr>
<td>PNH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other forms of hemolytic disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LEARNING OBJECTIVES

1. Red blood cells (RBC)
   - Life of a RBC
   - Hemoglobin
   - Sickle cell disease
   - Thalassemia Major
   - Chronic blood transfusion

2. Iron
   - Distribution of iron
   - Iron overload
   - Iron toxicity
   - Associated complications
   - Diagnosis
   - Treatment: Iron chelators
RED BLOOD CELLS

BONE MARROW

ERYTHROPOIESIS

Red blood cells = Erythrocytes

RBC FUNCTION

Oxygen transportation

O₂
HEMOGLOBIN

Each red blood cell contains several thousand hemoglobin molecules

Oxygen binds to iron on the hemoglobin molecule

Oxyhemoglobin: Hb + O₂ → HbO₂
THALASSEMIA MAJOR: NO $\beta$-CHAIN PRODUCTION

- Bone marrow ineffective erythropoiesis
- Severe anemia
- Iron absorption +++
- Iron overload
- Marrow expansion

Oxyhemoglobin: Hb + O$_2$ $\rightarrow$ HBO$_2$
SICKLE CELL DISEASE: MUTATION ON THE $\beta$-CHAIN

SICKLE CELL

Destruction

ANEMIA

Vaso-occlusion

Chronic Organ Damage

Oxyhemoglobin: $\text{Hb} + \text{O}_2 \rightarrow \text{HbO}_2$
SICKLE CELL DISEASE: TREATMENT

- **Treatment**
  - Vaso-occlusion prevention
    - Avoid cold, dehydration,…
  - Management of pain
  - Hydroxyurea
  - Transfusions
    - Only for severe complications
LEARNING OBJECTIVES

1. Red blood cells (RBC)
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   - Treatment: Iron chelators
IRON : NORMAL DISTRIBUTION

- Iron in
- Plasma iron pool
- Iron out
- 1–2 mg/day
- Skin
- Gut
- Menstruation
- Pregnancy

Total body iron = 4000 mg
Transferrin

Pietrangelo A. NEJM 2004; 350:2383-2397
IRON OVERLOAD

Iron In 200mg/unit
Iron Out 1-2 mg/day
Total body iron = 4000 mg

3U/month = 600mg/month → 7.2 g/year

Chelator
Iron
Iron In
Iron Out
CIRRHOSIS
COMPLICATIONS OF IRON OVERLOAD

Pituitary → impaired growth, infertility
Thyroid → hypothyroidism
Heart → cardiomyopathy, heart failure
Liver → hepatic cirrhosis, cancer
Pancreas → diabetes mellitus
Gonads → hypogonadism

In the absence of treatment
Damages are inevitable
→ Lethal complications
Liver Iron Concentration (LIC)

Percutaneous liver biopsy

Liver

A small slender core of tissue is removed with a biopsy needle

↑ Ferritin ≠ ↑ Iron burden
BUT
↓ Ferritin = ↓ Iron burden

Invasive

Noninvasive

Liver and cardiac MRI (Magnetic Resonance Imaging)
MAGNETIC RESONANCE IMAGING (MRI) = GOLD STANDARD

- Before treatment
- After treatment

Heart

Liver
TREATMENT: WHAT IS CHELATION THERAPY?

Chelator + Iron \rightarrow Chelate

Toxic

Chelator + Iron \rightarrow Excretion

With the courtesy of Dr Axelle Gilles
IRON CHELATION THERAPY IMPROVES SURVIVAL IN THALASSAEMIA

Well treated
Ferritin < 2500

Poorly treated
Ferritin > 2500

When to start chelation:
- Prior transfusions
- Evidence of chronic iron overload

After 120 mL/kg pRBC
(~ After 10-20 units)
OR
Serum ferritin > 800 - 1000 μg/L\(^1,2\)
(constantly)
OR
LIC ≥ 5 - 7 mg Fe/g dw\(^1,2\)

### TREATMENT: IRON CHELATING AGENTS

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose (mg/kg/day)</td>
<td>25–50</td>
</tr>
<tr>
<td>Route</td>
<td>sc, iv (8–12 hours, 5 days/week)</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 minutes</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, fecal</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Local reactions, Auditory, Ocular, Growth retardation, Allergy</td>
</tr>
<tr>
<td>Indication</td>
<td>Transfusional iron overload</td>
</tr>
</tbody>
</table>

Adapted from Brittenham GM. N Engl J Med 2011;364:146
## SIDE EFFECTS MANAGEMENT: DEFERASIROX

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>15-26%</td>
<td>Transient evening, with or after food</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Divide dose / ↓ dose then ↑</td>
</tr>
<tr>
<td>Diarrhea (! Lactose)</td>
<td>5 – 20%</td>
<td>Lactase / Loperamide /↓ dose</td>
</tr>
</tbody>
</table>

## Side Effects Management: Deferiprone

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<tbody>
<tr>
<td>Nausea, abd pain, diarrhea</td>
<td>3 – 25%</td>
<td>Transient</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>If not, Loperamide, ↓ dose</td>
</tr>
</tbody>
</table>

**Deferoxamine** and iron chelation therapy in thalassemia major and sickle cell disease. 

**Transfusional iron overload** and iron chelation therapy in thalassemia major and sickle cell disease. 
WHEN TO STOP CHELATION THERAPY?

- **Transfusion-dependent patients**
  - NEVER STOP CHELATION
  - Dose reduction if ferritin levels $< 1000 \mu g/L$
  - Avoid overchelation

- **Transfusion-independent patients**
  - Reduce dose if ferritin $< 1000 \mu g/L$
  - Stop chelation$^2$
    - Ferritin $\leq 300 \mu g/L$
    - LIC $\leq 3 \text{ mg Fe/g dw}$

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CONCLUSION: ADHERENCE TO CHELATION THERAPY

- **Adherence = Success**
- **Therapeutic alliance Doctor + Patient**
  - Involvement of patients in decisions → self-management
  - Reviews of results (MRI, ferritin levels…)
- **Administration**
  - prefer oral
- **Side effects**
  - Strict control
  - Monitoring → Prevention
  - Dose adjustment

Acute: simple transfusion

- Surgery (selected cases)
- Severe symptomatic anemia
  - Splenic sequestration
  - Severe or long-lasting aplastic crises
- Severe complications
  - Acute CNS stroke
  - Acute chest syndrome
  - Multiple-organ failure syndrome

### Thalassemia major

- **Transfusions**
  - 1st year of life
  - Chronic transfusion
    - $\text{Hb} > 9.5 - 10.5 \text{g/dL}$
- **Increased iron absorption**

→ **Higher and earlier iron load**
  - Growth / sexual dvp
  - Liver overload by 10 yo
  - Extra-hepatic iron spread
    - Heart, endocrine glands…

### Sickle cell disease

- **Transfusions**
  - Starts later
  - Transfusion regime
    - Top up $\leftrightarrow$ exchange
    - Sporadic $\leftrightarrow$ chronic
- **Less increased iron absorption**
- **Urinary iron loss (hemolysis)**

→ **Lower and later iron load**
  - No effect on growth
  - Less cardiac and endocrine involvement

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IRON TOXICITY

INFECTIONS ↔ TISSUES IRON OVERLOAD → CANCER

FREE RADICALS → OXIDATIVE DAMAGE

CELL DEATH – FIBROSIS

With the courtesy of Dr Axelle Gilles
IRON OVERLOAD – WORK UP

- **Pituitary** → LH, FSH, GH, ACTH
- **Para/Thyroid** → TSH, T3, T4 – PTH, D-Vit, Ca, P
- **Heart** → MRI T2*, LVEF, EKG
- **Liver** → MRI T2*, abdominal echography
- **Pancreas** → Glycemia, Oral Glucose Tolerance Test
- **Gonads** → Estradiol, Progesteron, Testosterone