Thalassemia

Diagnosis, Management and Nursing Implications

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Objectives

• Understand hemoglobin and the fetal switch
• Be able to differentiate the different types of thalassemia
• Understand how thalassemia is diagnosed
• Understand and goals of transfusion therapy
• Identify the pathophysiology, sequelae and treatment of iron overload
• State the challenges and side effects of chelation therapy – and strategies that can help patients.
• Identify nursing interventions to help patients and families across the lifespan
• Identify factors that can influence compliance
Disclosures

• Member of the Novartis Speaker Panel for Exjade and Jadenu

• Advisory Board member and speaker for Apo-pharma for Ferriprox

• Information will cover all current chelation therapies and will be fair and unbiased.

• Content will include off label use of pharmaceuticals
Hemoglobin

- To understand Thalassemia—must understand Hemoglobin
- Hemoglobin is a tetramer, composed of 2 pairs of globin chains, held together by the heme group—containing Fe.
- **Main function**: reversible transport of oxygen.
- As children and adults—Red Blood Cells containing hemoglobin are produced in the bone marrow—process called Erythropoiesis.
Hemoglobin

• 3 Major types of Hemoglobin
  – Hb A $\alpha\alpha/\beta\beta$
  – Hb A2 $\alpha\alpha/\delta\delta$
  – Hb F $\alpha\alpha/\gamma\gamma$

• all can carry O2

• have different life spans- present in blood in varying concentrations at different ages, and with different conditions.
  - Hemoglobin Electrophoresis with Quantitative A2 and F(HEP) – blood test to measure the amounts of each type of hemoglobin
Normal Red Blood Cells
# The Fetal Switch

<table>
<thead>
<tr>
<th>Types of cells</th>
<th>Megaloblast</th>
<th>Macrocyte</th>
<th>Normocyte</th>
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<tr>
<th>Part in the total synthesis of globin, %</th>
<th>Pre-and birth</th>
<th>Birth</th>
<th>Postnatal age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-similar globin chains</td>
<td>α</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>β-similar globin chains</td>
<td>ε</td>
<td>β</td>
<td>γ</td>
</tr>
</tbody>
</table>
Thalassemia: Characteristics

- a QUANTITATIVE anemia

- Autosomal recessive genetic mutation.

- The mutation causes a transcription error- the body can’t read the blue print to make globin chains.

- Type and severity depend on the defect, and the inheritance pattern.
Beta Thalassemia inheritance

- **When one parent is a patient and another a carrier**
  - Risk for child to:
    - Have Thalassemia: 50%
    - Become a carrier: 50%

- **When both parents are patients**
  - Risk for child to:
    - Have Thalassemia: 100%
    - Become a carrier: 0%

- **When one parent is a carrier**
  - Risk for child to:
    - Have Thalassemia: 0%
    - Become a carrier: 50%

- **When both parents are a carrier**
  - Risk for child to:
    - Have Thalassemia: 25%
    - Become a carrier: 50%
Thalassemia: Genetics

- Over 250-300 known mutations that cause thalassemia-type can determine severity.
- Patients can be homozygous for one mutation, or a compound heterozygote, resulting in disease.
- Beta globin chains: instructions on Chromosome 11 - $\beta/\beta$
- Alpha globin chains: Chromosome 16 $\alpha\alpha/\alpha\alpha$
Thalassemia Types

• **Thalassemia “Trait” aka “Minor”**
  - heterozygous for deletion
  - mild anemia, no disease

• **Thalassemia “Major” or “Disease”**
  - homozygous for deletion, or compound heterozygote.
  - usually require chronic transfusions for life

• **Non Transfusion Dependant Thalassemia (NTDT) or Thalassemia “Intermedia”**
  - these are patients who have thalassemia “disease” but due to lesser clinical severity, are not always dependant on chronic transfusions.
Beta Thalassemia

- mutation effects the production of beta chains
- Hb A αα/ββ
- 2 alpha chains
- 2 beta chains
- β+ Thal- makes Hb A
- β Zero Thal- does not make Hb A
- anemia after fetal switch
# The Fetal Switch

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<table>
<thead>
<tr>
<th>Prenatal age (weeks)</th>
<th>Birth</th>
<th>Postnatal age (weeks)</th>
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<tbody>
<tr>
<td>6</td>
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<td>12</td>
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<td>42</td>
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</tbody>
</table>

- **α-similar globin chains**
- **β-similar globin chains**
β Thalassemia

- Persons of Mediterranean, SEA, Indian, Pakistani, African, Middle Eastern descent
- Ineffective erythropoiesis
- β chains not produced
- Microcytic, Hypochromic anemia
- Relatively increased red cell count
- Trait:
  - Increased Hb-F (> 2.0%)
  - Increased Hb-A2 (>2.5-3.5%)
Thalassemia Trait Smear
Alpha Thalassemia

- Hb A, A2 and F are all made w/ alpha chains
- 4 sets of instructions to make 2 globin chains
- $\alpha\alpha/\alpha\alpha$
- Alpha Thalassemia major - anemia in utero - death in utero
  - Patients can survive if they receive intrauterine transfusions or are born prematurely.
**α Thalassemia**

- **Asian / African-American** descent/some Mediterranean
- **Hematologic findings depend upon how many of the four α globin genes are deleted**

<table>
<thead>
<tr>
<th>α₁</th>
<th>α₂</th>
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<td>α₁</td>
<td>α₂</td>
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</table>

- **normal**

<table>
<thead>
<tr>
<th>α₁</th>
<th>α₂</th>
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<tbody>
<tr>
<td>α₁</td>
<td>α₂</td>
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</table>

- **Silent carrier**
  - Normal hemogram

<table>
<thead>
<tr>
<th>α₁</th>
<th>α₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>x₁</td>
<td>α₂</td>
</tr>
</tbody>
</table>

- **CIS-Trait**
  - Microcytic-Hypochromic
  - Very Mild Anemia
  - Trans-Trait

<table>
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- **Hemoglobin H disease**
  - Microcytic-Hypochromic
  - Moderate-severe Anemia

<table>
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<th>α₁</th>
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- **Hydrops Fetalis**
  - Death *in utero*
The Fetal Switch

### Types of cells

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<tr>
<td></td>
<td></td>
<td></td>
<td>Bone marrow</td>
</tr>
</tbody>
</table>

### Graph

- **Axes**:
  - Y-axis: Part in the total synthesis of globin, %
  - X-axis: Prenatal age (weeks) and Postnatal age (weeks)

- **Lines**:
  - Blue line: α-similar globin chains
  - Red line: β-similar globin chains

- **Key Events**:
  - Birth (36 weeks)
  - Changes in globin synthesis from prenatal to postnatal phase.
Three gene deletion Hemoglobin H disease is a Thalassemia Intermedia syndrome.

- May have a fast migrating hemoglobin (HB H) on electrophoresis.
- Hb A2 and F are normal.
- Two gene deletion (trait) has a normal electrophoresis.
- Gene mapping is important in Asians for genetic counseling of parents.
How Thalassemia is Diagnosed

**Beta Thalassemia**
- DNA- gene mapping
  - Gold standard
  - *Useful* for genetic counseling
- HEP- can diagnose Beta thalassemia trait and major

**Alpha Thalassemia**
- DNA- Gene mapping
  - Gold standard
  - *Essential* for genetic counseling
- HEP- not effective
- will give false “normal” for alpha thalassemia trait
Thalassemia Trait: Treatment

• **NONE!!!!!**

• Iron will not correct the mild anemia.
• Patient requires genetic counseling at child bearing age.
• Advise parents to be worked up for Thalassemia trait… especially if they want to have more children
Thalassemia Major - Not Transfused

- Thalassemia Major Blood Smear
- Normal Blood Smear
Thal Major: Untransfused

- Anemia usually after 6 months
- Chronic low Hb in untransfused thalassemia patients lead to bone marrow hyperplasia
- Classic “Thal Facies” - maxillary and frontal bossing

- Very anemic (hb low as 3-4 g/dl) hepatosplenomegaly, poor growth, skeletal deformities, thal facies, cardiac failure.
- 80% of TM patients will die before age 5 if not treated
Beta Thalassemia Major -

Beta Thalassemia Major – bone changes
Beta Thalassemia Major

The face of thalassaemia

Facial deformities
Minimally treated patients aged 8 and 20 (Cyprus, 1940s)

Photos with permission (Modell and Berdoukas, 1984)
Treatment Options for Thalassemia Major (TM)

- **Three Major Treatment Options:**
  - **Medical Therapy - Transfusion and chelation**
  - Bone Marrow Transplant - matched sibling donor 90%
  - New Therapies: gene therapy, drugs to block ineffective erythropoiesis

- **NURSING INTERVENTION:** support the decisions of the team, provide education and support for the family, ensure the family understands their options
Thalassemia Major: Treatment

- Patients whose baseline Hb is < 7.5-8.5 gm/dl often require chronic transfusions.
- Patients are started on chronic transfusions based on different criteria:
  - S&S of clinical anemia
  - falling off the growth curve
  - excessive hyperplasia w/ extensive osteoporosis/osteopenia, bony changes
Goal of Transfusions

- Correction of anemia
- Suppression of erythropoiesis
- Transfused every 2-4 weeks with 10-20 cc/kg
- Goal baseline hemoglobin
  - Commonly accepted is 9-10 g/dl
  - Our practice >10.5 g/dl
- IDEAL: patients have RBC phenotyping done prior to transfusions
  - Screen for lesser antigens that can cause major antibodies in multiply transfused patients
  - Can be done using PCR technology on previously transfused patients
- Transfused with new, extended matched, leukofiltered PRBC
- Actual practice dependent on available resources.
Iron Overload

- Each 500 ml of blood deposits 200 mg of iron in the body—cannot be excreted.
- Iron deposits in the liver, heart, pancreas, thyroid, parathyroid, pituitary gland.
- Monitor endocrine, cardiac, hepatic function
- **Leading cause of death in patients with Thalassemia!!!**
Iron Toxicity ≈ Tissue Iron X Environmental Factors X Genetics X Time

Nursing Tip:
Iron is a silent killer. Educational needs are lifelong.
Measuring Iron

- **Direct measurements**
  - liver biopsy
  - MRI

- **Indirect measurements**
  - Serum ferritin

- **Invalid tools**
  - CT scan
  - Ultrasound.
Measuring Iron: Cardiac / Liver iron by MRI (T2*)

- The Gold Standard
- Excellent correlation with liver and cardiac iron
- The only reasonable way currently to measure heart iron.
- Cardiac iron is not related to liver iron
- Requires special software

Courtesy of Dr. John Wood
NTBI- The Real Culprit

NTBI

is a shorter form of
Non-transferrin-bound iron

by allacronyms.com
Liver iron does not directly correlate with cardiac iron

Black means high iron. In the MRI between A and B, the cardiac iron was high and the patient became adherent to chelation. Panel B shows the liver clears before the heart. (image courtesy of Dr J Wood)

Coates, TD, Free Radic Biol Med 2014
Cardiac T2* < 20 ms associated with low LVEF

LV = left ventricle; RV = right ventricle.

Relation of Cardiac T2* to Heart Failure

Pancreatic Fe precedes cardiac Fe

Measuring iron: Ferritin as a Monitor of Chelation

• Advantages
  - Can be measured with every clinic visit
  - Widely available
  - Can examine trends over time

• Disadvantages
  - Loose correlation with liver (body) iron
  - Wrong almost 30% of the time!
  - Increased with inflammation
  - Decreased if scurvy
  - Effect of chelation not linear
  - Different chelators may affect ferritin differently

DFO = deferoxamine.
When to start chelation

 Liver iron > 2-3 mgFe/gm dry weight as determined by MRI.
 Transfusions > 1 year or PRBC’s > 120cc/kg.
 Ferritin > 1000ng/ml
 Some now starting asap after initiation of chronic transfusions
Education: When to Start

• Diagnosis

• Chronic Transfusion Therapy:
  - Education at initiation of therapy and ongoing

• Intermittent transfusions:
  - Iron overload rarely discussed
  - Signs of iron overload after 10-20 units
  - Iron overload is not part of consenting process for blood transfusions
Overview of iron chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine (DFO)</th>
<th>Deferiprone (DFP)</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose</td>
<td>25–60 mg/kg/day</td>
<td>75-100 mg/kg/day</td>
<td>Exjade 20–40 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Jadenu 14-28 mg/kg/day</td>
</tr>
<tr>
<td>Route</td>
<td>s.c., i.v.</td>
<td>p.o.</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>8–12 h, 5 days/week</td>
<td>Liquid or tablet</td>
<td>Dispersion or tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 times daily</td>
<td>once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 min</td>
<td>3–4 h</td>
<td>8–16 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td>Approved indications</td>
<td>Treatment of chronic iron overload due to transfusion-dependent anaemias</td>
<td>Thalassaemia syndromes &gt;18 years 2nd line therapy in US,</td>
<td>Treatment of chronic iron overload due to frequent blood transfusions</td>
</tr>
</tbody>
</table>

s.c.= subcutaneous, i.v.= intravenous, p.o.= by mouth

Goals of treatment:
- Bind LPI / LCI
- Normalize Total body Fe
- Clear abnormal tissue Fe
- Restore organ function

All have the same fatal defect:
None of these are effective if the patient does not take them
Chelation Side Effects – Nursing Management

• **DFO**- site reactions, allergy, rash, lesions
  – Site rotation, hydrocortisone, warm packs, increased dilution

• **DFX**- nausea, vomiting, diarrhea, rash, elevation in AST/ALT, renal toxicities- inc Fanconi Syndrome, pancytopenia, allergy
  – Start lower dose and titrate up slowly
  – Dose reduction- or hold medication, take with food, mix with food, divide dose BID, take with lactaid or switch to Jadenu (if available)
  – Must have monthly CBC, Chem 14, urine p/c ratio done- and results followed closely. Hold dose for abnormal levels x2
Chelation Side Effects – Nursing Management

- **DFP** - nausea, vomiting, fatigue, arthralgia, neutropenia and agranulocytosis, elevations in ALT
  - Advise to start at 50% of dose and increase slowly over a few weeks
  - Hold if arthralgia, restart at lower dose and increase
  - Patients must have weekly CBCs to screen for neutropenia
  - If patient has a fever - they MUST
    - Hold the drug
    - Go to the ED - tell them they are on a medication that can cause neutropenia
Combination Chelation

• **Combination Chelation offers options for patients to:**
  – Maximize 24/7 coverage
  – Intensify chelation for severely overloaded patients
  – Minimize side effects
  – Enhance compliance

• **Sample “cocktails”**
  – **DFP/DFO** - most studied
    • DFP daily, with DFO 3-7 nights/week
  – **DFX/DFO** - some studies
    • DFX- daily- even low dose, with DFO 3-7 nights/week
  – **DFX/DFP** - some studies
    • DFP/DFX- both at full dose, or reduced depending on severity and tolerability

**Nursing Tip:** work with the patient and MD to find a combo that meets the needs of the patient and the highest likelihood of compliance.
LIC target: How low should you go?

- Normal LIC by MRI is about 1.2 mg / G dry weight liver.
- In thalassemia intermedia, morbidities are significantly greater if the LIC is > 7 mg / gm dw
- Cardiac morbidity is clearly related to T2* < 10 ms
- The overall mortality from cardiac deaths has dropped by 71% due in part to better chelation and the ability to monitor iron by MRI

In 2016, what should the LIC target of chelation therapy be?

In our opinion:
If resources are available to closely monitor chelation therapy, we should try to normalize LIC and eliminate iron overload from the heart and endocrine organs, especially in children.
Chelation- Overchelation

- **DFO**: truncal shortening, bone disease, auditory and ocular toxicities
- **DFX**: constipation, nausea, vomiting, renal tubular defects, alterations in electrolytes, elevations in AST/ALT

**Nursing Intervention**: Educate patients about dangers of overchelation: why monthly labs are so important, symptoms to look out for and who to call for concerns
Compliance

• Issue of compliance regardless of disease or medical regimen
Survival Benefit of Deferoxamine Is Highly Dependent on Compliance

Negative Factors and Compliance

• Lack of perceived importance**
• Side effects**
• No scheduled follow up**
  - Decayed adherence
  - Often ignored
  - Area for major improvement
• Contrasting health beliefs between patient and provider**
• Concerns about medication safety**

Nurse/Patient Communications

- Encourage honesty from your patient
  - Want to know if they aren’t taking it- so you can help them take it, and so you can keep a closer eye on them.

- Motivational Interviewing

- “Normalize” non-adherence

- There is no good method to measure compliance besides the MRI/biopsy
Positive Factors for Improved Compliance

• Sharing of responsibility between parent and patient = ↑ compliance*
• Perceptions of positive home environment*
• Perceived importance of medication**
• Scheduled follow ups**

*Treadwall et al, Ped Blood Ca, 2005
Thalassemia Major: Summary of Current Treatment

• Prior to blood transfusions, patients died before age 5
• Blood transfusions extended life through young adulthood
• Chelation therapy now provides for lifespan in 60s - depending on compliance with chelation
• Currently have 3 FDA approved chelators.
• Only cure for Thalassemia - Bone Marrow Transplant. - 10/10 matched sibling - 85% disease free survival.
• Gene Therapy - still “10 years” down the road - but trials are starting
• Nursing plays integral role in every aspect of care for thalassemia patients
Contact Information

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