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Iron overload in Clinical Practice

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What’s the fuss about the Iron economy?
Objectives

- Iron homeostasis/metabolism
- Causes of Iron overload
- Pathophysiology of iron overload
- Investigation of iron overload
  - Laboratory
  - Imaging
- Consequences of Iron overload
- Treatment options for iron overload
- Summary
Iron homeostasis/metabolism

• Iron homeostasis is a complex system that balances both the absorption of intestinal iron and release of stored iron, with the body’s iron requirements

• Several molecules, such as hepcidin, ferritin, and ferroportin provide tight regulation of this process, and contribute to iron homeostasis

• There is no regulated mechanism for the excretion of excess iron, therefore patients who require frequent blood transfusions become susceptible to developing chronic iron overload
This is the Iron economy: Tightly controlled process

Iron absorption from the intestine:
Regulation of iron metabolism: Hepcidin

Hepatic bacteriocidal protein

Low hepcidin
- Iron uptake
  - Ferritin
  - Fpn
  - Fe

Iron-exporting cells (duodenal enterocytes, macrophages, hepatocytes)

High hepcidin
- Iron uptake
  - Ferritin
  - Fpn

Hepcidin
- Iron release into plasma
  - Fe
Causes of iron overload

• Primary (Hereditary)
  • It results from a primary defect in the regulation of iron balance

• Secondary (Acquired causes)
  • Mainly associated by clinical conditions requiring repeated packed RBC transfusions for example in hemolytic anemia (Thalassemia, Sickle cell disease (SCD)), myelodysplasia (MDS)
  • Ineffective erythropoiesis
  • Toxic ingestion
Transfusion related iron overload

- Repeated transfusions resulting in increased circulating iron
- Increased saturation of transferrin
  - Increased NTBI and LPI
    - NTBI and LPI enter tissues and form ROS causing lipid peroxidation and end organ damage

Each unit of PRBC 200-250 mg of iron
Pathological mechanisms and consequences of iron overload

IRON CHELATION

LABILE IRON

- NEOPLASIA
- ANTI-APOPTOTIC

NF-κB ACTIVATION

ROS

Capsase activation
DNA damage
Geometric instability

Lipid peroxidation
Organelle damage
Lysosomal fragility

Enzyme leakage

CELL DEATH

BLOOD TRANSFUSION
HIGH IRON ABSORPTION
INFECTION
TGF-β1

Collagen synthesis
FIBROSIS
Mechanism of end organ damage by iron overload

- NTBI (Non-Transferrin-Bound Iron) can be taken up and either controlled or uncontrolled, leading to labile iron.
- Labile iron can be used metabolically or cause reactive oxygen species (ROS), leading to organelle damage, lipid peroxidation, or storage in ferritin.
- Lipid peroxidation can lead to TGF-β1, which promotes fibrosis.
- Cell death can also occur due to organelle damage.
- Export pathways can help in removing iron from the system.
EFFECTS OF IRON OVERLOAD

Iron overload →
Capacity of serum transferrin to bind iron is exceeded

Non-transferrin-bound iron (NTBI) circulates in the plasma

\[ \text{O}_2^- + \text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{OH}^- + \text{HO} \]

Excess iron promotes the generation of free hydroxyl radicals, propagators of oxygen-related tissue damage (Fenton Reaction)

Insoluble iron complexes are deposited in body tissues and end-organ toxicity occurs

Cardiac failure  Liver cirrhosis/fibrosis/cancer  HSC senescence  Diabetes mellitus  Infertility  Growth failure
Serum Ferritin Concentration

• Advantages:
  • Noninvasive
  • widely available
  • useful in deciding when to initiate therapy
  • useful in monitoring treatment effectiveness

• Disadvantages:
  • Measurement values altered by inflammation, infection, and Vitamin C deficiency
  • does not correlate well with total body iron

• Sustained ferritin levels greater than 2500 mcg/L are associated with organ toxicity and death (Olivieri NF et al, N Engl J Med. 1994;331:574-8)
Liver Biopsy: Gold standard

• The “Gold Standard”
• Advantages: Correlates well with total body iron burden
• Allows for assessment of liver histology,
• Predictor of risk for cardiac disease, endocrine complications and death

• Disadvantages: Invasive, Potentially risky
Magnetic Resonance Imaging

- Several imaging techniques are used to estimate liver and cardiac iron deposition
- Non invasive
- Correlates well with liver iron concentration by biopsy
- Disadvantages: Expensive, variety of techniques and analytical programs may limit comparability, cardiac disease may be present when liver iron levels are low

Bright = high iron concentration; dark areas = low iron concentration
Iron overload in thalassemia

- Transfusion-related iron overload in the major mechanism in transfusion dependent thalassemia (TDT) resulting from multiple PRBC transfusions
- Ineffective erythropoiesis, noted in patients with non-transfusion-dependent thalassemia (NTDT) syndromes, can also result in clinically relevant iron overload, despite lack of regular blood transfusions primarily due to increased gastrointestinal (GI) absorption.
- Tissue iron deposition can begin within 1-2 years but clinically evident cardiac or hepatic dysfunction may not occur till 10 or more years from the initiation of transfusion therapy
Time frame on effect of iron overload: Lessons from thalassaemia

- Hepatic fibrosis → Cirrhosis
- Cardiomyopathy
- Hypoparathyroidism
- Hypothyroidism
- Diabetes
- Hypogonadism
- Arrhythmia
Iron overload in Sickle Cell disease (SCD)

• Regular red cell transfusion therapy increasingly is being used in the management of children with SCD

• Indications for episodic or chronic blood transfusion include: primary or secondary prevention of stroke, Acute chest syndrome, Poorly controlled pain crisis, severe anemia due to aplastic crisis or sequestration

• Cardiac iron loading, iron-related cardiomyopathy and endocrinopathies are less common in SCD than in thalassemia

• Exchange transfusion can be employed to limit iron loading in patients with SCD but is not generally utilized in thalassemia

Iron overload in MDS

• A heterogeneous group of clonal disorders of hematopoietic stem cells, characterized by ineffective hematopoiesis leading to peripheral cytopenias and hypercellular bone marrow, with increased propensity to progression to acute myeloid leukaemia

• Supportive red blood cell transfusions represent a life-saving treatment for patients with chronic anemia, in particular for those who do not respond or have a poor response to available treatments

• Transfusions lead to iron overload, with an increased risk of associated comorbidity and mortality, independently of the underlying hematological disease, in relation to iron toxicity to cardiac, hepatic and endocrine cells

• Adequate iron chelation therapy can, however, improve survival and may delay transformation into acute myeloid leukaemia

Iron overload impairs survival in MDS

Malcovati, Haematologica, 2006
Iron overload in Oncology

• Blood product transfusions, including red blood cell transfusions, are supportive care measures which are important in the tolerability of the therapy of cancer.

• Oncology patients receiving numerous red blood cell transfusions are not routinely screened or evaluated for risk of iron overload or its consequences.

• A retrospective blood bank records review was performed of pediatric hematology/oncology patients treated for a period of 2003-2013 to identify those patients receiving >10 packed red blood cell (PRBC) transfusion,
  • 34.7%) were identified as receiving >10 PRBC transfusions
  • 27% patients had a serum ferritin level that was obtained
  • All the patients (100%) with a serum ferritin result had a serum ferritin level >1000 ug/L (range 1048-22021).
  • Only one patient (off-therapy sarcoma patient, serum ferritin =1788 ug/L) was on therapy for iron overload (Exjade and phlebotomy).

Identifying Iron Overload in Pediatric Oncology Patients, Nicole Giamanco, Anne, B. Warwick and Gary Crouch, Blood 2014 124:2682;
Treatment of Iron overload

• Regular phlebotomy- extensive experience, proven efficacy but cannot be used patients with anemia or poor venous access

• Erythracytapharesis
  • Manual
  • Automated

• Iron chelation- 3 drugs currently approved for use, They include: Deferoxamine, deferiprone and deferasirox

• Investigational: Hepcidin agonists

What is Chelation Therapy?

Chelator + Metal → Non-Toxic Chelator → “Chelate” → Outside the Body

Metal Chelator + Toxic

What is Chelation Therapy?
## Indications for Iron chelation therapy by disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk/Intermediate- I MDS</td>
<td>&gt;20 pRBC transfusions, SF&gt;1000-2500ug/L and life expectancy &gt;1year</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>&gt;120cc of pRBC/kg plus SF &gt;1000ug/L or liver iron &gt;7mg Fe /g dry weight</td>
</tr>
<tr>
<td>Beta thalassemia</td>
<td>&gt;2-3years of transfusions and LIC &gt;5mg Fe /g/dry weight</td>
</tr>
<tr>
<td>Diamond Blackfan anemia</td>
<td>After &gt;15 pRBC transfusions or &gt;2years, with an aim to keep the ferritin level between 1000-1500ug/L and LIC &lt;7mg Fe/g dry weight</td>
</tr>
<tr>
<td>NTDT</td>
<td>LIC &gt;5mg Fe /g dry weight and serum ferritin &gt;300mgug/L</td>
</tr>
</tbody>
</table>
Treatment of Iron overload: Choice of Iron chelation therapy

- Serum ferritin (ng/mL)
- LIC (mg/g dw)
- Cardiac T2* (ms)

- 1,000 → 2,500
- 3 → 7

□ Maintain existing therapy

- No cardiac dysfunction
- Cardiac dysfunction

□ DFO over 12 h for 7 days/week
□ DFO over 24 h for 7 days/week
□ DFX at maximum tolerated dose

LIC: Liver Iron concentration, DFO: Deferoxamine, DFX: Deferasirox
<table>
<thead>
<tr>
<th>Variable</th>
<th>Deferoxamine</th>
<th>Deferasirox</th>
<th>Deferiprone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelator-iron complex</td>
<td>Hexadentate, 1:1 complex</td>
<td>Tridentate, 2:1 complex</td>
<td>Bidentate, 3:1 complex</td>
</tr>
<tr>
<td>Usual dose</td>
<td>25–50 mg/kg/day</td>
<td>20–40 mg/kg/day</td>
<td>75–100 mg/kg/day</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous or intravenous, 8–10 hr/day, 5–7 days/wk</td>
<td>Oral, once daily</td>
<td>Oral, three times daily</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>20–30 min</td>
<td>8–16 hr</td>
<td>2–3 hr</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Biliary and urinary</td>
<td>Predominantly biliary</td>
<td>Predominantly urinary</td>
</tr>
<tr>
<td>Regulatory approval</td>
<td>Approved in United States, Canada, Europe, and other countries</td>
<td>Approved in United States, Canada, Europe, and other countries</td>
<td>Not approved in United States or Canada; approved in Europe and other countries</td>
</tr>
<tr>
<td>Indication</td>
<td>Transfusional iron overload</td>
<td>Transfusional iron overload</td>
<td>Transfusional iron overload in patients with thalasemia major, when deferoxamine therapy is contraindicated or inadequate</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Irritation at the infusion site, ocular and auditory disturbances, growth retardation and skeletal changes, allergy, respiratory distress syndrome with higher-than-recommended doses\textsuperscript{12}</td>
<td>Gastrointestinal disturbances, rash, increase in serum creatinine level; potentially fatal renal and hepatic impairment or failure, gastrointestinal hemorrhage\textsuperscript{13}</td>
<td>Agranulocytosis and neutropenia; gastrointestinal disturbances, arthropathy, increased liver-enzyme levels, low plasma zinc level, progression of hepatic fibrosis associated with increase in iron overload or hepatitis C\textsuperscript{11}</td>
</tr>
</tbody>
</table>
Summary

• Iron overload in clinical practice is often an under recognized cause of morbidity and mortality of patients undergoing chronic PRBC transfusions

• Monitoring for iron overload can be done by taking a transfusion history, laboratory and imaging studies which help estimate total body iron burden

• Treatment of iron overload involves phlebotomy, erythrocYTEapheresis and iron chelation

• Oral iron chelators provide a way to get rid of toxic iron deposited in organs at risk and prevents or reverses organ damage
Thank you...