IRON DEFICIENCY / ANAEMIA

ANTHONY BEETON
HYPOXIA

Iron metabolism involves the conversion of heme iron into nonheme iron, which is then transported and regulated by factors such as hypoxia (HIF-2), Heme transporter, and iron regulatory proteins (IRP). Iron is stored in ferritin and released as labile iron. The process is crucial for maintaining iron homeostasis.
Body iron ± 3 – 4 g

Liver and the reticuloendothelial system and spleen (approximately 200 – 300 mg in adult women and 1 g in adult men)

Cells contain small concentrations in iron-containing proteins

Erythrocyte haemoglobin (2–3 g)

Muscle contains iron predominantly in myoglobin (300 mg).
IRON PHYSIOLOGY

- TOXICITY
  - FREE IRON / LABILE IRON POOL
  - FERROUS (2+)
- “100 HUNGRY ENZYMES”
- FERRITIN – IRON STORE INDICATOR
- ANAEMIA A LATE PRESENTATION IN I.D.
IRON DEFICIENCY

• SEQUENCE OF EVENTS
  • USE OF IRON STORES WITH NORMAL HAEMATOPOIESIS
  • INEFFICIENT ENERGY METABOLISM IN ALL CELLS ESPECIALLY MUSCLE (FATIGUE)
  • MAKING SMALLER CELLS WITH NORMAL HB CONC (MICROCYTOSIS – MCV)
  • MAKING SMALL CELLS WITH REDUCED HB CONC (HYPOCHROMIA – MCHC)
  • MAKING FEWER CELLS
IRON PHYSIOLOGY TESTS

• INDIRECT – HB; MCV; MCHC; RETIC COUNT; RDW ETC. ETC.

• DIRECT
  • SERUM IRON
  • FERRITIN
  • TRANSFERRIN SATURATION ($T_{\text{SAT}}$)
ANAEMIA

• 1/3 OF WORLD’S POPULATION (2.36 BILLION PEOPLE)
  • HIGHER IN AFRICA
  • SASOS 47.8% ANAEMIA
    • INDEPENDENT PREDICTOR OF DEATH & AKI
  • WOMAN OF CHILD BEARING AGE / CHILDREN
  • > 50% OF ANAEMIA IS IDA
  • ID CO-EXISTS WITH MANY OTHER ANAEMIAS
  • ANAEMIA ASSOCIATED WITH ADVERSE OUTCOMES – DEATH; ORGAN DYSFUNCTION & TRANSFUSION

• ID FAR COMMONER THAN IDA
• COMMONEST DISEASE IN THE WORLD
• ORAL IRON CHEAP BUT NOT RELIABLE AND SLOW TO WORK WITH MANY S/E S
TRANSFUSION

• ONLY FOR SYMPTOMATIC OXYGEN DELIVERY DEFICIT
  • NO LIFE SUSTAINING SUBSTITUTE AVAILABLE

• AROUND 1 – 1.5% OF SOUTH AFRICANS ARE DONORS

• BLOOD USAGE INVERSELY PROPORTIONAL TO UNDERSTANDING OF TRANSFUSION (PATHO)PHYSIOLOGY

• ~ 11.8% OF RED CELL TRANSFUSIONS INDICATED

• FIXES BLOOD TESTS NOT NECESSARILY PATIENTS
TRANSFUSION

• PATHOPHYSIOLOGY
  • VOLUME OVERLOAD
  • IMMUNOLOGICAL EFFECTS – TRAIL; TRIM
  • INFECTION – IMMUNOLOGICAL; FREE IRON / HAEM
  • STORAGE INJURY – CYTOKINES; PROCOAGULANTS; HAEM; FREE IRON
  • POOR OXYGEN DELIVERY
    • LEFT SHIFT IN OLD RBC
    • POOR MICROVASCULAR FLOW
    • POORER DO₂ AT HIGHER HB AFTER BANKED BLOOD TRANSFUSION
TYPICAL IDA PICTURE

• MICROCYTIC HYPOCHROMIC ANAEMIA
• FERRITIN < 30 NG/ML
• TRANSFERRIN SATURATION < 20%
ID - MISCONCEPTIONS

1. A NORMAL FERRITIN EXCLUDES IDA
   • WIDE RANGE OF NORMAL VALUES (~40 – 500 NG/ML)
     • < 30 NG/ML – **ALWAYS** IRON DEFICIENCY
   • FERRITIN – ACUTE PHASE REACTANT – RELEASED BY LIVER IN INFLAMMATORY STATES
   • LEVELS OF 30 – 100 WITH EVIDENCE OF INFLAMMATION (CRP) USUALLY ID
     • CHECK $T_{sao}$ – IF < 20% = ID
   • LEVELS OF > 100 WITH MICROCYTOSIS / HYPOCHROMIA
     • DEFECT OF IRON UTILIZATION
     • USUALLY NEED IRON WITH ERYTHROPOIETIN (EPO)
   • IRON THERAPY AT HIGHER FERRITIN LEVELS – CCF; CKD; CANCER – ALL TEND TO HAVE ELEVATED HEPCIDIN & INTESTINAL ABSORPTION / STORAGE RELEASE BLOCK
2. NON ANAEMIC ID DOES NOT NEED INTERVENTION
   • HUGE IRON DEFICIT BEFORE HB FALLS
   • FATIGUE & EFFORT INTOLERANCE PRESENT BEFORE ANAEMIA
   • PROVEN BENEFIT FOR IRON THERAPY
     • ATHLETES
     • BLOOD DONORS
     • PREGNANT / MENSTRUATING WOMEN (ID - MATERNAL / FOETAL ADVERSE EFFECTS)
     • CANCER (DECREASED THROMBOSIS VIA NORMALIZATION OF PLATELET SYNTHESIS)
     • CCF (ENERGY; QOL; SURVIVAL)
     • PERI-OPERATIVELY (ID PREDISPOSES TO INFECTION / TRANSFUSION / FATIGUE)
     • IRON DEFICITS 1 – 2 G – DIFFICULT TO CORRECT ORALLY
3. **ORAL IRON IS ALWAYS EFFICACIOUS IF TOLERATED**
   - DEFICITS OF > 1 G
   - CAN ABSORB < 5MG/DAY – 200 DAYS + TO CORRECT (HB RISES NOT > 0.7 MG/DL/MONTH)
   - NEED TO CONTINUE FOR 3 MONTHS AFTER CORRECTION OF IDA TO REPLENISH IRON RESERVES
   - > 70% INTOXERANCE AT DOSES > 100 MG/DAY
   - PPI / ANTACIDS INHIBIT ABSORPTION
   - BEST APPROACH FOR TOLERABILITY (GREATEST % ABSORPTION)
     - LOW DOSES
     - BD DOSES
     - ALTERNATE DAYS
   - THE ONLY INDICATION IS COST
ID - MISCONCEPTIONS

4. IV IRON SHOULD BE RESERVED FOR SEVERE ANAEMIA
   • CRITICAL ANAEMIA REQUIRES BLOOD TRANSFUSION UNTIL HAEMODYNAMICS / ISCHAEMIA RESOLVE
   • MUST BE FOLLOWED BY IV IRON FOR MAXIMUM EFFICACY
   • IV SUPERIOR TO ORAL IN EVERY SITUATION AND COST IS THE ONLY INTERFERING VARIABLE
     • WELL TOLERATED
     • RAPID, SUSTAINED EFFECT AFTER 1 – 2 DOSES
     • NO HB OVERSHOOT (UNLIKE EPO)
     • MANY SAFE FORMULATIONS
ID - MISCONCEPTIONS

5. THERE IS NO NEED FOR FOLLOW UP AFTER IRON REPLETION

- IV IRON
  - WELL-BEING IMPROVES AFTER 2 – 3 DAYS
  - RETICULOCYTE COUNT INCREASES IN A WEEK
  - HB RISES FROM 1 – 2 WEEKS AFTER INFUSION
  - MAXIMUM RESPONSE IN 4 – 6 WEEKS
- SHOULD RE-ASSESS AFTER 6 – 8 WEEKS WHERE IV IRON NO LONGER CONFOUNDS TESTS
- MUST REASSESS BECAUSE MOST UNDERLYING CAUSES CONTINUE (MALIGNANCY; GI INFLAMMATION AND BLEEDING; CKD; CCF)
6. ALL IV IRONS ARE THE SAME

- All can produce rapid correction of ID and IDA
- Originators shown to be superior over some generics
- FCM has most evidence and is uniquely indicated in CCF
- Side effects related to high % labile iron (e.g., iron sucrose or gluconate and iron dextrans) and the presence of dextran
- FCM / Iron isomaltoside - minimal S/E s as low free iron and high sugar binding
  - Can be administered fast (15 – 30 min)
  - Still monitor q15min and for 30 min after conclusion but largely mythology
Table I - Characteristics of different intravenous iron formulations.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Iron gluconate&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Iron sucrose&lt;sup&gt;7&lt;/sup&gt;</th>
<th>LMWID&lt;sup&gt;8&lt;/sup&gt;</th>
<th>Ferric carboxymaltose&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Iron isomaltoside 1000&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Ferumoxytol&lt;sup&gt;11&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Molecular weight (kDa)</td>
<td>289-440</td>
<td>30-60</td>
<td>165</td>
<td>150</td>
<td>150</td>
<td>750</td>
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<tr>
<td>Labile iron (% injected dose)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3.3</td>
<td>3.5</td>
<td>2.0</td>
<td>0.6</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Maximal single dose (mg)</td>
<td>125</td>
<td>200</td>
<td>20 mg/kg</td>
<td>20 mg/kg (max 1,000 mg)</td>
<td>20 mg/kg</td>
<td>510</td>
</tr>
<tr>
<td>Infusion time for 1,000 mg (min)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>720</td>
<td>300</td>
<td>180*</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Product cost per 1,000 mg (€)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-</td>
<td>112</td>
<td>103</td>
<td>192</td>
<td>192</td>
<td>162&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Administration cost per 1,000 mg (€)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>554</td>
<td>231</td>
<td>139</td>
<td>35</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>Total cost per 1,000 mg dose (€)</td>
<td>-</td>
<td>342</td>
<td>242</td>
<td>227</td>
<td>227</td>
<td>232</td>
</tr>
</tbody>
</table>
ID - MISCONCEPTIONS

7. IV IRON HAS A HIGH INCIDENCE OF SIDE EFFECTS
   • SEVERE ANAPHYLAXIS RARE < 1:250 000 (15 – 20 TIMES LOWER THAN RBC TRANSFUSION)
   • FISHBANE REACTIONS RESEMBLING ALLERGY OR MYALGIA / ARTHRALGIA MORE COMMON AND ARE GENERALLY SELF LIMITING WITHOUT THERAPY – RELATED TO LABILE IRON
     • CHOICE OF AGENT – FCM LOWEST
     • APPROPRIATE DILUTION
     • SPEED OF ADMINISTRATION
   • TRYPTASE
   • INFUSIONS MUST STILL BE DONE IN MEDICALLY REGISTERED AND RESOURCED ENVIRONMENTS
   • BENEFIT FAR OUTWEIGHS RISK
   • DEATHS ASSOCIATED WITH IV IRON USUALLY MULTIFACTORIAL (CCF; SEPSIS; CANCER)
   • HYPOPHOSPHATAEMIA ASSOCIATED PREDOMINANTLY WITH FCM – RELATED TO DECREASED RENAL REABSORPTION AND INCREASED FIBROBLAST GF LEVELS. WORSE WITH VIT D DEFICIENCY. CLINICAL RELEVANCE?
8. PREMEDICATIONS REDUCE INFUSION REACTIONS
   • ANTIHISTAMINE CAUSE FAR MORE S/E S THAN THEY PREVENT
     • SOMNOLENCE; HYPOTENSION; BRADYCARDIA ETC
   • CHECK TRYPTASE TO DETECT TRUE ALLERGY – FOR FUTURE REFERENCE
   • MULTI-ALLERGIC / ASTHMATIC PATIENTS MAY BENEFIT FROM A SHORT COURSE OF PERI-INFUSION STEROID
ID - MISCONCEPTIONS

9. IV IRON INCREASES THE RISK OF INFECTION / OXIDATIVE STRESS
   • BACTERIA THRIVE ON ELEMENTAL (FREE / LABILE) IRON
     • HIGHEST LEVELS WITH TRANSFUSION
     • MODERATE LEVELS WITH CHRONIC / REPEATED IRON THERAPY
     • SHORT TERM IV IRON RISK ~ PLACEBO
     • ANY IRON THERAPY CONTRA-INDICATED IN SEVERE SYSTEMIC SEPSIS – EVIDENCE FREE ZONE
     • CHRONIC IRON THERAPY – ADVISABLE TO USE LOW DOSES (FCM < 400 MG/MONTH)
     • SEPSIS RISK FROM ID OR IDA IS ORDERS OF MAGNITUDE HIGHER THAN THAT FROM FREE SERUM IRON
   • OXIDATIVE STRESS – SIMILAR CONCERNS WITH CHRONIC IRON THERAPY
     • USE AGENTS WITH LOWEST FREE IRON CONCS AND AT LOWEST EFFECTIVE DOSES
10. IS ADJUVANT IRON NECESSARY IN PATIENTS ON EPO WITH NORMAL FERRITIN?

- PATIENTS WITH INFLAMMATORY ANAEMIA / ANAEMIA OF CHRONIC DISORDERS / FUNCTIONAL IRON DEFICIENCY E.G. CKD MAY RESPOND TO EPO SINCE IT:
  - REDUCES HEPcidin
  - ENHANCES IRON ABSORPTION
- EPO PRODUCES RAPID HAMATOPOIESIS
  - IRON DEMANDS HIGH AND IV IRON IS MANDATORY OTHERWISE "APPARENT" EPO RESISTANCE
  - IRON ALSO REDUCES THROMBOCYTOSIS AND VTE
  - IDEALLY GIVE IV IRON (E.G. FCM 1000MG) BEFORE EPO
PERI-OPERATIVE MANAGEMENT OF ID / IDA

• ASSESS IRON STATUS ON INITIAL PRESENTATION
  • FBC & RETICULOCYTES
  • SERUM IRON; FERRITIN; T_{SAT}

• IF OVERT ID / IDA / INFLAMMATION WITH FERRITIN < 100 NG/ML
  • IV FCM / ISOMALTOSIDE 1000 MG SINGLE INFUSION OR 500 MG X 2 (<50 KG)
    • IDEALLY > 3 WEEKS PRE-OP BUT ANY TIME BETTER THAN NO INFUSION
    • REASSESS HB; RETICULOCYTES 3 WEEKS AFTER IRON INFUSION AND IF HB NOT INCREASED > 2 G/DL, REPEAT INFUSION + EPO
    • REASSESS 3 WEEKS POST-OP IN CASE FURTHER SUPPLEMENTATION REQUIRED
CASE STUDY

- 50 YEAR OLD FEMALE MEDICAL DOCTOR
- LARGE RETROPERITONEAL TUMOUR
- PRESENTED WITH FATIGUE AND HB OF 9.7 (IRON DEFICIENT)
- SURGERY DEEMED URGENT BUT NOT EMERGENT
- IV FCM 1G GIVEN 18 DAYS BEFORE SCHEDULED SURGERY
- HB ON DAY OF SURGERY 13.9
- SURGERY WITH CELL SALVAGE
  - BLOOD LOSS 2200ML – 900 ML SALVAGED BLOOD RETURNED WITH HCT OF 46%. NO BANKED BLOOD
  - DISCHARGED HOME WITH HB 10.8
PATIENT BLOOD MANAGEMENT

- Anaemia management is a cornerstone of PBM
- The toxicity of iron therapy is largely mythology
- The benefit of transfusion for management of anaemia is entirely mythology
- PBM is a non-negotiable intervention for better patient outcomes and optimal resource management