Red Blood Transfusion in clinical practice

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Blood Units collection

• Every year about 75 million units of blood are collected worldwide

Where the blood goes?
Who does blood go to in England?

A. Wells on behalf of the Eastr study - 2007
(Epidemiology and Survival of Transfusion Recipients)

<table>
<thead>
<tr>
<th></th>
<th>RBC</th>
<th>Plasma</th>
<th>platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>9.142</td>
<td>4.232</td>
<td>3.584</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>69</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>Male(%)</td>
<td>44</td>
<td>64</td>
<td>58</td>
</tr>
</tbody>
</table>
| Major surgery(%)    | 40      | 45      | 35
Who uses blood in France? results of a cross-sectional and nationwide survey

J.F. Quaranta et al.

pour le Group Receveurs de la Société Française de Transfusion Sanguine

• 3.450 patients
• Indications:
  – 50.9% onco-hematology
  – 23.2% major surgery
  – 16.7% emergency and internal medicine

> 50% of the patients aged => 70 yrs old
What the characteristics of patients who require blood transfusion?

D. Rigamonti, P. Lanzini, R. Parolo, C. Velati
Blood Transfusion 2008; 6, Suppl 1, S127

Out of 4,708 transfused patients,:
2.163 (46%) for major surgery  2.545 (54%) non surgery need.

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>Pts in IM units (%)</th>
<th>Pts in surgery units (%)</th>
<th>Total n. of pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 20</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>21 - 40</td>
<td>3</td>
<td>6</td>
<td>4.5</td>
</tr>
<tr>
<td>41 - 60</td>
<td>10</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>61 - 80</td>
<td>48.5</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>&gt; 81</td>
<td>38</td>
<td>31</td>
<td>34.5</td>
</tr>
</tbody>
</table>
Indications for RBC transfusion

- Still controversial
- RBC transfusion is administered most often to surgical and intensive care patients
- Most studies assessing transfusion thresholds are non-randomized cohort studies, the results of which should be interpreted cautiously
Transfusion during intensive care
TRICC study (NEJM 1999)

• Liberal transfusion group: Hb 10-12g/dl
• Restrictive transfusion group: Hb 7-9gr/dl

outcome
• No significant difference was found in all cause of mortality at 30 days in ICU
• The group with lower hemoglobin had a lower rate of myocardial infarction and congestive hearth failure

Hebert PC et al. N.Engl J Med 1999; 340,409-17
Vincent JL et JAMA 2002, 288:1499-507
1. Adhere to a restrictive transfusion strategy (7-8g/dl) in hospitalized, stable patients (strong recom; high quality evidence)

2. Adhere to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease and considering transfusion for patients with symptoms or Hb level of =<8g/dl (weak recom; moderate quality evidence)

3. No recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with ACS (uncertain recomm; very low-quality evidence)

4. Transfusion decisions be influenced by symptoms and Hb concentration (weak recomm; low-quality evidence)

Transfusion Guidelines
AABB (American Association of Blood Bank)

• Instead of following a strict number for transfusion threshold based on Hb, the physician at bedside should treat the patient and clinical situation
• A symptomatic patient with symptoms from anemia - whether with dyspnea, chest pain, or poor distal perfusion - likely warrants transfusion, as does the patient actively hemorrhaging with hemodynamic instability
FOCUS
(Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair)

• No benefit to reducing mortality or improvement in ambulation with a restrictive (8g/dl) vs liberal (10g/dl) transfusion threshold

Cochrane reviews (restrictive threshold 7g/dl)

• reduced in hospital mortality (RR 0.74)
• reduced total mortality (RR 0.80)
• reduced rebleeding (RR 0.64)
• reduced pulmonary edema (RR 0.48)
• reduced bacterial infection (RR 0.86)

Holst LB et al. BMJ 2015; 350:1354
BMJ meta-analysis
(31 trials, 9813 patients)

• No difference in mortality, morbidity, or myocardial infarction when comparing liberal and restrictive transfusion strategy.

• They did find a reduced incidence of infection with a restrictive transfusion strategy

Holst Lb et al BMJ 2015; 350: 1354
Choosing Wisely
ASH

- Don’t transfuse more than the minimum number of red blood cell units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7-8 g/dl in stable, non-cardiac in-patients)

released December 4, 2013
References

• Red cell transfusion in clinical practice.

• Best clinical practice: Red blood cell transfusion in the emergency department
Iron Deficiency anemia

• In patient with severe iron deficiency anemia: would you prescribe oral or iv iron supplementation as first choice?

• In patients with low level of serum iron and high ferritin would you prescribe iron supplementation?
Prevalence of anaemia by aetiology

Physiological iron turn-over

**Dietary iron**
- Duodenum (average, 1-2 mg/day)

**Utilisation**
- Other iron-containing enzymes (100mg)
- Bone marrow (300mg)
- Sloughed mucosal cells, desquamation, menstruation, other blood loss

**Storage iron**
- Liver parenchyma (1000mg)
- Muscle (myoglobin) (300mg)
- Muscle

**Plasma transferrin (3mg)**

**25 mg/day**

**Iron loss**
- 1-2 mg/day

Hepcidin: The master regulator of iron homeostasis

Liver 1000 mg ≈600 mg
≈2000 mg

Ganz T, Physiol Rev 2013
ID and ID(A): Definition

**Iron Deficiency**
- Depleted iron stores

**Iron Deficiency Anaemia**
- Depleted iron stores
- Haemoglobin (Hb) concentration falls below defined lower limit (12g/dl for women, 13 g/dl for men)

**Absolute Iron Deficiency** (no iron stores)
- Low Transferrin Saturation (TSAT<20%)
- Serum ferritin low (<20ng/ml – or <100ng/ml in case of inflammation)
- Elevated Serum Transferrin Receptor (sTfR)

**Functional Iron Deficiency** (full iron stores but ID in erythroid bone marrow)
- Low TSAT (TSAT<20%)
- Serum ferritin normal or elevated (>20 ng/ml – or >100ng/ml in case of inflammation)
- Normal sTfR

Adapted from Hush R. and Schaefer R. Pocket Atlas Special. Thiene 2006 and Prof. IY. Beguin oral communication. Parallel Symposia at EHA congress 2014, Milan, Italy
ID and ID(A): Causes

**Iron Deficiency**
- Absolute Iron Deficiency
- Functional Iron Deficiency

**Blood Loss**
- Heavy menstrual bleeding
- Delivery
- Gastrointestinal disorders/bleeding
- Surgery
- Blood donation
- Haemodialysis

**Decreased Iron Intake**
- Poor diet
- Vegetarian/vegan diet
- Disease-related anorexia
- Eating disorders

**Increased Iron Demand**
- Infancy
- Adolescence
- Pregnancy
- Endurance sport

**Decreased Iron Absorption and utilisation/released**
- Inflammatory bowel disease
- Chronic or malignant disease
- Interaction with food components
- Concomitant intake of other drugs
- Malabsorption

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When **history** (menometrorrhagia, symptoms of peptic ulcer disease) and preliminary **laboratory data** (low MCV, low MCH, high RDW, increased platelet count) support this diagnosis.

Plasma levels of:

- Iron
- Iron binding capacity (transferrin)
- Transferrin saturation
- Ferritin should be measured
Defining Anemia in the elderly

✓ Classic WHO criteria for defining anemia: Hb < 13 g/dL in males and Hb < 12 g/dL in females.

✓ Hb values in apparently healthy elderly individuals are generally lower than those in younger adults, and the differences between males and females tend to disappear with aging.

✓ Hb < 12 g/dL now commonly considered indicative of anemia in ELDERLY of both sexes (Andrè E, Geriatr Gerontol Int 2013)
IDA in elderly: caveats in lab diagnosis

Classic workup for IDA:

<table>
<thead>
<tr>
<th>Iron Stores</th>
<th>Serum Ferritin (μg/L)</th>
<th>TIBC (μg/dL)</th>
<th>SI (μg/dL)</th>
<th>Saturation (%)</th>
<th>Marrow Sideroblasts (%)</th>
<th>RBC Protoporphyrin (μg/dL)</th>
<th>RBC Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50-200</td>
<td>&gt;360</td>
<td>50-150</td>
<td>30-50</td>
<td>40-60</td>
<td>30-50</td>
<td>NL</td>
</tr>
<tr>
<td>1-3+</td>
<td>&lt;20</td>
<td>&gt;380</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>0-1+</td>
<td>&lt;15</td>
<td>&gt;400</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td>&lt;10</td>
<td>&gt;100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td>&lt;30</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>Microcytic/hypochromic</td>
<td></td>
</tr>
</tbody>
</table>

Serum ferritin increases with age (and confounded by inflammation).

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## Prevalence of anemia in elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (Years)</th>
<th>Population</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrucci, Guralnik, Bandinelli, et al (2007)</td>
<td>&gt;70</td>
<td>Community-dwelling elderly Italian</td>
<td>11</td>
</tr>
<tr>
<td>Denny, Kuchibhatla, Cohen (2006)</td>
<td>≥71</td>
<td>Community-dwelling</td>
<td>24</td>
</tr>
</tbody>
</table>

*World Health Organization anemia criteria: hemoglobin <13 g/dL for adult men and <12 g/dL for adult women.
†In this study, anemia defined as hemoglobin <11.5 g/dL.
NANES III study

• Incidence of anemia >65 yrs:
  - men 11%
  - women 10%

• Etiology
  - 1/3 nutritional deficiency
  - 1/3 anemia of inflammation
  - 1/3 “unexplained” anemia

• Ethnic differences:
  - 3 times higher in non-ispanic black vs non ispanic white

Causes of anemia in the elderly

At least 20-25% of anemias in elderly is due to Iron Deficiency, which often concur in remaining cases.
GI diseases: the most frequent causes of IDA in elderly

The bad triad: Malnutrition-Malabsorption-Blood Loss

**Malnutrition**
Inadequate dietary iron intake

**Evaluation of patient's nutritional status**

**Upper GI blood losses**
Esophagitis, gastritis, ulcers, cancer or pre-malignant lesions, angiodysplasia, (antithrombotic drugs)

**Evaluation of risk factors for cancer, fecal occult blood test, gastroscopy (VCE for small bowel)**

**Malabsorption**
HP infection, AAG, CD, IBD, drugs (PPI).

**Search fecal antigen of HP, screening for AAG and/or CD, gastroduodenoscopy**

**Lower GI blood losses**
Colon-rectal cancer or pre-malignant polyps, IBD, ano-rectal lesions (e.g. hemorrhoids), angiodysplasia (antithrombotic drugs)

**Evaluation of risk factor for cancer, fecal occult blood test, colonoscopy**

Busti F, Front Pharmacol 2014
## Diagnostic workup for acquired IRIDA

<table>
<thead>
<tr>
<th></th>
<th>H pylori</th>
<th>Autoimmune gastritis</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td>H pylori IgG antibodies or fecal antigen</td>
<td>Serum gastrin</td>
<td>Tissue transglutaminase IgA Abs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-parietal Abs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-intrinsic factor Abs</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td>Urease breath test</td>
<td>Gastroscopy and biopsies (optional)</td>
<td>Duodenal biopsy, HLA screening for DQ2 or DQ8 genotypes</td>
</tr>
<tr>
<td></td>
<td>Gastrosopicy and biopsies (optional)</td>
<td>(recommended)</td>
<td></td>
</tr>
<tr>
<td><strong>Response to specific treatment</strong></td>
<td>H pylori eradication</td>
<td>N.A.</td>
<td>Gluten-free diet</td>
</tr>
</tbody>
</table>
Celiac Diseases increasingly recognized in elderly

Figure 1.
Increased in the incidence rate of celiac disease in people older than 60 years of age over a 56-year period in Olmsted County, Minnesota (1950-2006); Incidence rate= new cases of CD per 100,000 person-years, adjusted to the US 2000 white population.
IDA in elderly: a case paradigm

- S.A. aged 70
- Unexplained IDA since 2006
- FOB intermittently +
- EGDS -
- Colon endoscopy –
- Virtual colonscopy -
- Multiple transfusions (last yr)

Angiodysplasia in the ascending colon (WCE)
Available treatment options

Oral Iron

VS

i.v. Iron
Oral iron therapy

• **200 mg** iron per day

• **Ferrous salts**: Ferric compounds less absorbed (better tolerated)

• Absorption **improves** when given between meals
  Absorption **decreases** with inflammation, renal failure, cancer, poor transit...

• Duration of regimen: **3–6 months**
  – Anemia corrects with first 3 months
  – Iron Stores get replenished with second 3 months

• Tolerance **improves** when given with meals
  Side effects: **GI** (intolerance, diarrhea, constipation, black stools...)

IY. Beguin oral communication Parallel Symposia at EHA congress 2014, Milan, Italy.
## Causes of Oral Therapy Failure

### Causes of treatment failure in oral iron therapy

- Lack of adherence to therapy or insufficient length of therapy for the degree of iron deficit
- Concomitant/causal underlying blood loss pathology not resolved
- Poor duodenal absorption:
  - Concomitant GI pathology (inflammatory bowel disease or any other cause or chronic inflammation; malignancy)
  - Insufficient gastric acidity (pharmacological blockade of gastric secretion)
  - Chemical inhibition of absorption (lead-aluminum)
- Side effects:
  - Nausea
  - Constipation
  - Upper GI irritation
- Iron-refractory iron deficiency anaemias (IRIDA)
## Indications for i.v. Iron

<table>
<thead>
<tr>
<th>Main indications for IV iron treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer related anaemia</td>
</tr>
<tr>
<td>Post-partum iron deficiency anaemia</td>
</tr>
<tr>
<td>Anaemia of pregnancy</td>
</tr>
<tr>
<td>Anaemia of chronic kidney disease</td>
</tr>
<tr>
<td>Anaemia of inflammatory bowel disease</td>
</tr>
<tr>
<td>Anaemia in patients treated in an intensive care unit</td>
</tr>
<tr>
<td>To increase blood donation before surgery in elective orthopedic patients</td>
</tr>
<tr>
<td>In iron malabsorption syndromes (post gastrectomy, Biermer disease, IRIDA)</td>
</tr>
<tr>
<td>Intolerance of or non-compliance with oral iron treatment</td>
</tr>
<tr>
<td>Severe iron deficiency anaemia with continuous bleeding (Osler-Weber-Rendu disease)</td>
</tr>
</tbody>
</table>
Advances on i.v. iron

Iron Core

Carbohydrate shell

1947: Fe-Saccharide
1954: Fe-Dextran (HMW)
1999: Fe-Gluconate
2000: Fe-Sucrose
2009: Ferumoxytol
2011: Fe-Carboymaltose
Iron toxicity (limiting dose) depends on stability of the iron/carbohydrate complex.

\[
\text{Fe}^{+++} + \text{T} = \text{Toxicity}
\]

\[
\text{T} = \text{Transferrin}
\]

\[
\text{Fe}^{+++} + \text{T} = \text{Free Iron}
\]
Features of new Fe(III)-hydroxide carbohydrate complexes

- Highly stable complexes, do not release large amounts of ionic iron
- “Similar” to ferritin
- Macrophage uptake
# Intravenous iron compounds

<table>
<thead>
<tr>
<th>Iron Gluconate</th>
<th>Iron Sucrose</th>
<th>Ferumoxytol</th>
<th>Iron Carboxymaltose</th>
<th>Iron Dextran</th>
<th>Iron Isomaltoside</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum single iron dose</strong></td>
<td>125 mg*</td>
<td>200 mg**</td>
<td>510 mg</td>
<td>20 mg/kg bw*** (1000 mg)</td>
<td>20 mg/kg bw</td>
</tr>
<tr>
<td><strong>Route for maximum dose</strong></td>
<td>Injection or infusion**</td>
<td>Injection</td>
<td>Injection or infusion</td>
<td>Infusion</td>
<td>Infusion</td>
</tr>
<tr>
<td><strong>Time for maximum dose</strong></td>
<td>Infusion: 1 hour</td>
<td>Infusion: 30 min</td>
<td>Injection: 17 sec</td>
<td>Infusion: 15 min</td>
<td>Infusion: 4–6 h</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>Max 3 times a week</td>
<td>Max 3 times a week</td>
<td>3–8 days</td>
<td>Weekly</td>
<td>2–3 times a week</td>
</tr>
</tbody>
</table>

*125 mg can be administered in some countries
**500 mg can be administered in some countries
***only for infusion, 15 mg/kg bw for injection

Prof. Y. Beguin oral communication. Parallel Symposia at EHA congress 2014, Milan, Italy. Table generated from single product’s SmPC.
Iron Sucrose  
(Venofer)

- Preparations contain 20 mg iron/mL

- Approved for IV use only

- Safety and efficacy profile similar to that of ferric gluconate (dialysis, non-dialysis CKD, IBD, chemotherapy-induced anemia, peripartum period, gastric bypass, heavy uterine bleeding...)

- Test dose not indicated, but recommended in patients who are sensitive to iron dextran or have other drug allergies
Iron Sucrose
Venofer

• **Recommended dose:**

  – Anemic **cancer** patients receiving **erythropoiesis-stimulating agents** is **200 mg** infused over 60 minutes, repeated every two to three weeks

  – It is routinely given as a **200 mg** IV bolus over two minutes in **dialysis** centers

• While approved as a 500 mg infusion over longer periods of time (hours), single doses greater than 300 mg are **not recommended**
Ferric Carboxymaltose
Ferinject

• **Novel** stable iron complex for IV use

• Can be given at **single doses** of up to **1000 mg** of elemental iron per week over a recommended infusion time of **15 minutes**

• A number of trials have shown **efficacy and safety** of this agent in iron deficient patients in a number of different settings (eg, heavy uterine bleeding, postpartum women, chronic renal failure, inflammatory bowel disease, heart failure, nonresponse to oral iron)

• It was shown to be effective in **alleviating symptoms of congestive heart failure** and was the first agent to demonstrate **efficacy** in **chemotherapy-associated anemia** when administered **without** concomitant use of an **erythropoiesis-stimulating agent**
Ferric Carboxymaltose
Ferinject®

- **Licensed** for use in Europe, Asia, and New Zealand

- **Approved** for use in the United States in patients with **IDA** and *intolerance or unsatisfactory* response to oral iron and for treatment of **IDA** in adults with **nondialysis-dependent** CKD

- Based on the preponderance of published evidence, ferric carboxymaltose is **safe and effective**, with a **side effect** profile **similar** to the **other** available intravenous iron formulations