# EM CASES SUMMARY

## Episode 65 –IV Iron for Anemia in Emergency Medicine

*With Dr. Walter Himmel, Dr. Jeannie Callum and Dr. Yulia Lin*

Prepared by Dr. Michael Kilian, edited by Dr. Anton Helman, May 2015

For years we've been transfusing red cells in the ED to patients who don't actually need them. A study looking at trends in transfusion practice in the ED found that about 1/3 of transfusions given were deemed totally inappropriate. As we explained in previous EM Cases episodes, there have been a whole slew of articles in the literature over the years that have shown that morbidity and mortality outcomes with lower hemoglobin thresholds, like 70g/L for transfusing ICU patients (TRICC trial), patients in septic shock (TRISS trial), and patients with GI bleeds are similar to outcomes with traditional higher hemoglobin thresholds of 90 or 100g/L. We're simply transfusing blood way too much! The American Association of Blood Banks in conjunction with the American Board of Internal Medicine's Choosing Wisely campaign, as one of its 5 statements on overuse of procedures, stated, "don't transfuse iron deficiency without hemodynamic instability".

So, our goals here are to give you an understanding of why it's important to avoid red cell transfusions in certain situations, why IV iron is sometimes a better option in a significant subset of anemic patients in the ED, and the practicalities of exactly how to administer IV iron.

## Case 1:

ID: 49 year old woman sent in by her family physician with a note indicating *"severe menorrhagia for several months and hemoglobin 57 g/L, please transfuse".*
PMH: Nil
HPI: Decreased exercise tolerance with increasingly heavy periods for several months. She denies dizziness or syncope.
O/E: Vitals and exam all within normal limits

**How you would manage this patient's anemia?**

## Is severe anemia unsafe in healthy people?

In a study of healthy subjects from JAMA in 1998 entitled 'Human Cardiovascular and Metabolic Response to Acute Severe Isovolemic Anemia', in which aliquots of blood (450-900 mL) were removed to reduce blood hemoglobin concentration from 131g/L to 50 g/L and isovolemia was maintained with 5% human albumin and/or autologous plasma, they found that acute isovolemic reduction of blood hemoglobin concentration to 50 g/L did not produce evidence of inadequate systemic "critical" oxygen delivery, as assessed by lack of change of O2 and plasma lactate concentration. Analysis of Holter readings suggested that at this hemoglobin concentration in this resting healthy population, myocardial ischemia would occur infrequently.

## Compensation in chronic vs acute anemia

Patients with chronic anemia can adjust physiologically to anemia even more readily than patients with acute anemia because of the shift in the oxygen dissociation curve. This is facilitated by a change in the 2,3-DPG level allowing the RBCs to be 'less selfish' so they can more easily offload oxygen to the tissues. As such, a hemoglobin of 50g/L can be considered as physiologically higher than it appears in patients with chronic anemia.

## The WOMB Trial showed that young women can safely tolerate a hemoglobin as low as 50g/L

The WOMB trial was a multi-centered Dutch trial that enrolled 521 women with severe postpartum anemia (hemoglobin 48 to 79 g/L) who were randomized to transfusion or transfusion only if they developed severe symptoms. It found no differences in any important outcomes (recovery of hemoglobin, 6 week hemoglobin). There was, however, a non-clinically significant difference in fatigue scores at 7 days that was not persistent at later time point. 517 units were transfused to the "transfused group" vs. 88 for the group for only severe symptoms.

## Alloimmunization is the most important and under-recognized risk associated with red cell transfusions

Perhaps the most important and under-recognized risk of red cell transfusions is *allo-immunization* among women of childbearing age.

Allo-imunization, which has a rate of 8% per transfusion in young women, involves the development of antibodies against red blood cells, which in future pregnancies can cross the placenta and precipitate hemolytic disease of the newborn in women who have received previous transfusion, can render the patient ineligible for an organ transplant if required and can make them unmatchable for future transfusions.

Think of a blood transfusion as a *blood transplant*: When you give someone a blood transfusion, you are changing their immune system for life. Red cell transfusions should not be thought of as a delivery system for iron!

Other risks of packed red blood cell transfusions include a 1/700 risk of TACO (Transfusion Associated Circulatory Overload) a 1/10,000 risk of TRALI (Transfusion Related Lung Injury) and a 1/40,000 risk of an acute hemolytic transfusion reaction.

## Indications for Iron

The American Society of Anesthesiologists recommended against RBC transfusions in young, healthy patients without ongoing blood loss and a hemoglobin >60 g/L, unless they are symptomatic or hemodynamically unstable. Symptoms to screen for include chest pain, SOB, pre-syncope, lightheadedness, hypotension and tachycardia.
Fatigue, pallor and reduced exercise tolerance are NOT, in and of themselves, an indication for red cell transfusion.
The trigger for transfusion related to “ongoing blood loss” will depend on acuity of blood loss, volume of ongoing bleeding and hemodynamic instability.

### Indications for IV Iron:

1. Oral iron poorly tolerated or failure of oral trial
2. Poor oral absorption (ie. gastric bypass, celiac disease, gastritis)
3. Rate of bleeding too brisk for oral iron
4. Severe anemia (Hb <90g/L) especially if ongoing bleeding
5. Time-sensitive pressures (OR etc.)

The main contraindications to IV Iron are active systemic infection (eg: suspected sepsis) since iron is a good microbial nutrient, and a known allergic or hypotensive reaction in the past.

## Risks of IV Iron

1. Hypotension (1-2%)
2. Serious allergic reactions (< 1 in 1,000,000)

Other more common adverse reactions include joint aches, muscle cramps, headache, chest discomfort, nausea, vomiting and diarrhea, which generally resolve spontaneously within 24hrs of administration of IV iron.

## Administering IV Iron

The product you choose will depend on the dose you want to give, how quickly you want to deliver it and the side-effect profile (see order set example at end of summary)

| | Iron Sucrose (Venofer) | Ferumoxytol (Feraheme) |
|---|---|---|
| **Dose (Max)** | **300 mg in 250 ml NS** | **510 mg in 17 ml (add to 50 ml NS)** |
| **Infusion Time** | **2 hrs** | **15 min – 60 min** |
| **Serious hypersensitivity** | **.6 per $10^6$ (FDA 2001-2003)** | **< .5% (<5 in 1000)** |
| **Cost** | **$120 (same mg per mg)** | **$200** |

Patients with the following **risk factors** should receive **slower infusions** (e.g. Feraheme® [ferumoxytol] over 60 minutes or Venofer® [iron sucrose] 300mg over 2 hours)

- Age > 65 yrs
- Baseline systolic BP less than 100
- Severe asthma or eczema
- Severe respiratory or cardiac disease
- Treatment with beta-blockers, ACE inhibitors or 3 or more anti-hypertensive medications
- Nephrology patients

After IV Iron, and with ongoing oral supplementation, a patient's hemoglobin will start to rise 3-7 days after the IV infusion. You can expect a 1-2 point rise in the hemoglobin per day, and after 2-4 weeks the hemoglobin will have risen 20-30g/L.

### Oral Iron supplementation after IV Iron:

Ferrous sulfate 300mg 1 tab QHS: contains 60mg of elemental iron

- Take at bedtime on empty stomach at least 2 hours after meals with Vitamin C 500mg
- Avoid taking with calcium or magnesium supplements as these decrease absorption.

## Lab Interpretation to determine iron deficiency

**IDA Definition**

Hb < 120 g/L (females)

Hb < 130 g/L (males)

**AND**

MCV ≤ 75 fL (with previously normal MCV documented)

**OR** Ferritin ≤ 30 µg/L (w/in 6 months of visit)

| | Iron deficiency Anemia | Thalassemia |
|---|---|---|
| Hb | Low | Low (100-115) |
| MCV | < 85: Consider Fe deficiency<br><75: Fe deficiency | Low (60's) |
| RBC Count | Low | High |
| RDW | High | Normal |
| Ferritin | Low (<30) | |

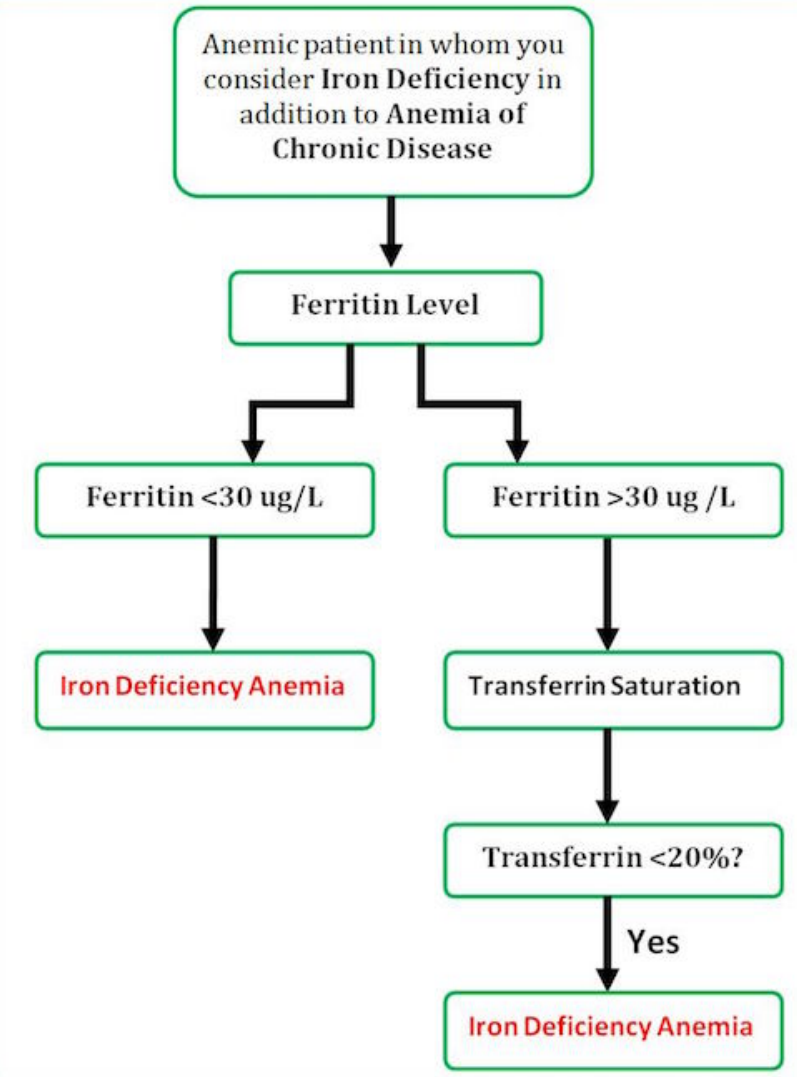
Patients with thalassemia may also have iron deficiency contributing to their anemia. If a patient with thalassemia has a Ferritin <30, consider them iron deficient.

## Case 2:

ID: 85 year old male from nursing home sent in for "*usual red cell transfusion*" which he receives on a monthly basis.
HPI: Patient denies chest pain, shortness of breath, palpitations, dizziness or melena
PMH: CHF, CRF
Hb= 65 g/L

### Would you transfuse this patient with RBCs?

Most of the patients in the ED found to be anemic are elderly. These patients generally fall into one of three categories: One third will have a simple nutritional deficiency (iron or B12). One third will have anemia secondary to a chronic disease. The rest of the patients will have an undifferentiated cause of their anemia that will require further investigation.
For an elderly patient with multiple comorbidities it can be challenging to determine if their anemia is secondary to iron deficiency as well as anemia of chronic disease. To you help differentiate and decide whether a patient would benefit from IV iron and supplementation, our experts have suggested the following approach:




## Case 3:

ID: 82 year old woman with a mechanical fall at home. She was unable to stand up and called EMS, who noted an externally rotated and shortened right leg.
PMH: Diabetes, hypothyroidism, hypertension, hypercholesterolemia, B12 deficiency anemia (non compliant with treatment)
HPI: Has had fatigue and SOBOE which has been unchanged for months. She denies chest pain.
O/E: Vitals within normal limits, no orthostatic changes.
Initial blood work reveals a Hb= 83 g/L in ED.
After speaking with the orthopedic surgeon on call, they request that you transfuse 2 units of pRBCs in preparation for the OR.

Do you order a pRBC transfusion for this patient?

## Which pre-operative patients require red cell transfusions?

The FOCUS trial sought to determine whether a higher threshold for blood transfusion would improve recovery in patients who had undergone surgery for a hip fracture. They showed that even among elderly patients with known coronary artery disease or multiple coronary risk factors,

there was less mortality post-operatively at 30 and 90 days among patients with a transfusion trigger of 80 g/L compared to those with a higher transfusion trigger.

Observational studies of the use IV iron pre-operatively for patients with anemia have shown a reduced rate of red cell transfusion required.

## Key References: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Sunnybrook Health Sciences Centre

## INTRAVENOUS IRON THERAPY (Venofer® or Feraheme© or Iron Dextran)

### INDICATIONS & CRITERIA FOR USE

**Intravenous iron** may be used to treat iron deficiency defined as:

1. Hb < 110 AND either of 2 or 3 below
2. Ferritin < 30; OR
3. Ferritin < 200 AND iron saturation < 20%

**Venofer®** dosage: Usually 300 mg in 250mL NS by IV infusion over 2 h. If weight < 50 kg (110 lb), consider a 200 mg dose to reduce infusion-related side effects.

**Feraheme®** dosage: 510 mg diluted in 50 mL NS by IV infusion over 15 min

**Iron Dextran** dosage: The initial infusion requires a test dose of 25mg administered over 15 minutes with physician in the patient care area for the first 30 minutes of the infusion. If test dose is tolerated, then administer dose (500mg -1000mg) diluted in 250-1000 mL over 2-6 hours. Subsequent infusions may include Total Dose Infusion (TDI) (see Iron Dextran IV Drug Monograph)

| Indications & Criteria for Use | Venofer® Regimen | Feraheme® Regimen |
|---|---|---|
| Inadequate response to an adequate trial of oral iron* | 1 dose and reassess in 4 weeks | 1 dose and reassess in 4 weeks |
| Nephrology: inadequate response to an adequate trial of oral iron * | 300 mg IV weekly x 3 doses | 510 mg weekly x 2 doses |
| Inability to absorb oral iron resulting in severe iron deficiency (ferritin < 30) caused by GI disease (celiac) or surgery (gastrectomy) (maintain ferritin > 50 with IV iron) | Typically 1 dose per month | Typically 1 dose per month |
| Severe intolerance to oral iron (vomiting and/or diarrhea) | 1 dose and reassess in 4 weeks | 1 dose and reassess in 4 weeks |
| Chronic GI bleeding with inadequate response to an adequate trial of oral iron* and GI interventions (as needed to maintain hemoglobin > 110 g/L) | Typically 1 dose per month. Titrate to lowest possible frequency | Typically 1 dose per month. Titrate to lowest possible frequency |
| Rapid correction of anemia in patients with severe symptomatic iron deficiency anemia (Hb < 90 g/L) in whom avoidance of RBC transfusion is important | 1 dose and reassess in 4 weeks | 1 dose and reassess in 4 weeks |
| During chemotherapy or radiation therapy for cancer | Hb 90-109 g/L – 1 dose<br>Hb < 90 g/L – 2 doses given 2-4 weeks apart | Hb 90-109 g/L – 1 dose<br>Hb < 90 g/L – 2 doses given 3-7 days apart |
| Preoperative iron deficiency anemia before elective **high blood loss surgery** | Hb <130 g/L – 1 dose<br>Hb < 110 g/L – 2 doses given 1-2 weeks apart | Hb <130 g/L – 1 dose<br>Hb < 110 g/L – 2 doses given 3-7 days apart |

* An adequate trial of oral iron therapy consists of the following:

- Duration of 3 months
- Adequate dose – 200 mg/day of elemental iron given as ferrous fumarate 300 mg po BID; if not tolerated, consider Proferrin (heme iron polypeptide) 11 mg po BID
- Vitamin C to enhance iron absorption – 500 mg with each dose of iron
- Optimal time of administration: on an empty stomach (1 hr before breakfast and at bedtime)

November 4, 2014

COMPLETE ABOVE ALLERGY BOX AT TIME OF INITIAL ORDERS

| YES | NO | | Physician Must Check Off Appropriate Orders |
|---|---|---|---|
| ■ | ■ | | Diagnosis: ..... |
| | | 1 | **iron sucrose (Venofer®)** - Select one of the following doses:<br>Patient weighs at least 50 kg (110 lb)<br>300 mg in NS 250 mL by IV infusion over 2 hours<br>every ..... ☐ Months ☐ Weeks x ..... doses<br>**OR**<br>Patient weighs less than 50 kg (110 lb)<br>200 mg in NS 250 mL by IV infusion over 2 hours<br>every ..... ☐ Months ☐ Weeks x ..... doses |
| | | 2 | **ferumoxytol (Feraheme®)** 510 mg<br>Contraindications:<br>• Ferumoxytol is contraindicated in patients with an allergy to any drug<br>• EXCEPTION: A physician may, at his/her discretion, decide to continue ferumoxytol therapy in a patient with drug allergies who has previously tolerated the drug (i.e., received at least 2 infusions of ferumoxytol without incident)<br>• Pregnancy and breastfeeding (iron sucrose [Venofer®] is the IV iron of choice)<br>Dose: 510 mg diluted in NS 50 mL every ..... ☐ Months ☐ Weeks x ..... doses<br>☐ Infuse over 15 min (routine)<br>☐ Infuse over 60 min in the following:<br>• Age greater than 65 yrs<br>• Baseline systolic BP less than 100<br>• Severe asthma or eczema<br>• Severe respiratory or cardiac disease<br>• Treatment with beta-blockers, ACE inhibitors or 3+ anti-hypertensives<br>• Nephrology patients<br>☞ Physician to ask patient if an **MRI is scheduled** – see ferumoxytol IV monograph |
| | ■ | 3 | **Prescription for Venofer® or Feraheme® has been faxed to** (select one):<br>☐ Outpatient Pharmacy M1 FAX: 4503<br>**OR**<br>☐ Odette Cancer Centre Pharmacy (if Rx written by OCC physician) FAX: 9-416-480-7809 |
| | ■ | 4 | **FAX this form to location where patient will be infused** (select one):<br>☐ Transfusion Medicine Clinic MG551; FAX: 5764<br>☐ Surgical Short Stay Unit (Blood Conservation patients) MG503; FAX: 4128<br>**Laboratory Test Results:** Hemoglobin ..... g/L<br>Ferritin ..... mcg/L<br>Transferrin saturation ..... percent<br>Date of labwork results (YYYY/MM/DD): ..... |

**Physician's Signature:** **PRINT NAME:** **Pager:**