Ontario Naturopathic Integrative Network
Connecting Care, Elevating Practice

Intravenous Iron Protocol

Rationale

Iron deficiency is very common in the adult population and can lead to anemia and a host of other non-hematological sequelae. Patients experiencing symptoms of iron deficiency should have a full work up to determine presence of deficiency and, where possible, the cause.

Approved Clinical Indication for Intravenous Use

Oral iron therapy is suitable for most patients and is the most effective first line treatment in patients. However, there are many situations where intravenous iron therapy is most appropriate. These include:

- Contraindications to oral iron, or compliance or tolerance (side effect) issues
- Pregnancy (beyond the first trimester) and postpartum if oral iron not suitable or effective, or to prevent physiological decompensation
- Comorbidities which may impact on absorption (e.g. Intestinal mucosal disorders), or bone marrow response
- Chronic kidney disease receiving erythropoiesis-stimulating agent therapy
- Ongoing iron losses that exceed absorptive capacity
- Requirement for rapid iron repletion (e.g. prevention of physiological decompensation or preoperatively for non-deferrable surgery)

Contraindication for use

- Hypersensitivity to product or any component of the formulation
- Serious hypersensitivity to other parenteral iron products,
- Decompensated liver cirrhosis or active hepatitis;
- Non-iron-deficiency anemia (e.g. hemolytic anemia);
- Iron overload (e.g. hemochromatosis; hemosiderosis);
- History of multiple allergies
- 1st trimester of pregnancy

Hypersensitivity reactions are the most concerning reactions with iron infusions. Factors which predispose a patient to increased risk of hypersensitivity to iron infusions include:

- Previous reaction to intravenous iron infusions
- Fast iron infusion rate
- History of other drug allergy or allergies
- Severe asthma or eczema
- Mastocytosis
- Severe respiratory or cardiac disease
- Older age
- Treatment with beta blockers or ACE inhibitors
- Systemic inflammatory disease (e.g. Rheumatoid Arthritis, Lupus, etc.)
- Anxiety
- Pregnancy (first trimester)

Side Effects

- Hypotension
- Headache
- Nausea
- Muscle Cramps
- Skin rash
- Hypophosphatemia
- Skin Tatooing

Managing Complement Activation Related Pseudo-allergy (CAPRA or Fishbane) Reactions to Iron Infusion

A **Fishbane reaction** is a rare, non-life-threatening adverse reaction to intravenous (IV) iron administration. It is characterized by symptoms such as **chest pain, back pain, flushing, myalgia, and arthralgia**, often resembling a hypersensitivity reaction but typically **not involving hypotension or respiratory distress**. It is thought to be caused by labile iron reacting with complement before being bound to transferrin. It is not life threatening, is often seen at the beginning of an infusion, can occur in patients who have previously tolerated IV iron and will self-resolve. If a Fishbane reaction is suspected:

1. Pause the infusion and continue to administer 0.9% sodium chloride at KVO rate
2. Reassure the patient and continue to assess the patient over the next 15 minutes. CAPRA reactions will self-resolve in that time. If no resolution occurs,

consider other hypersensitivity and address according to the hypersensitivity protocol below.

3. After 15 minutes and symptom resolution, discuss rechallenging with the patient and, if the patient consents, resume the infusion at 50% of the speed previously administered.
4. If this is well tolerated, increase flow rate slowly
5. Stop infusion if symptoms recur

Managing Hypersensitivity Reactions to Iron infusions

Please review the algorithm
Refer to Figure 1 for hypersensitivity treatment algorithm. Please note the following doses of emergency therapeutics:

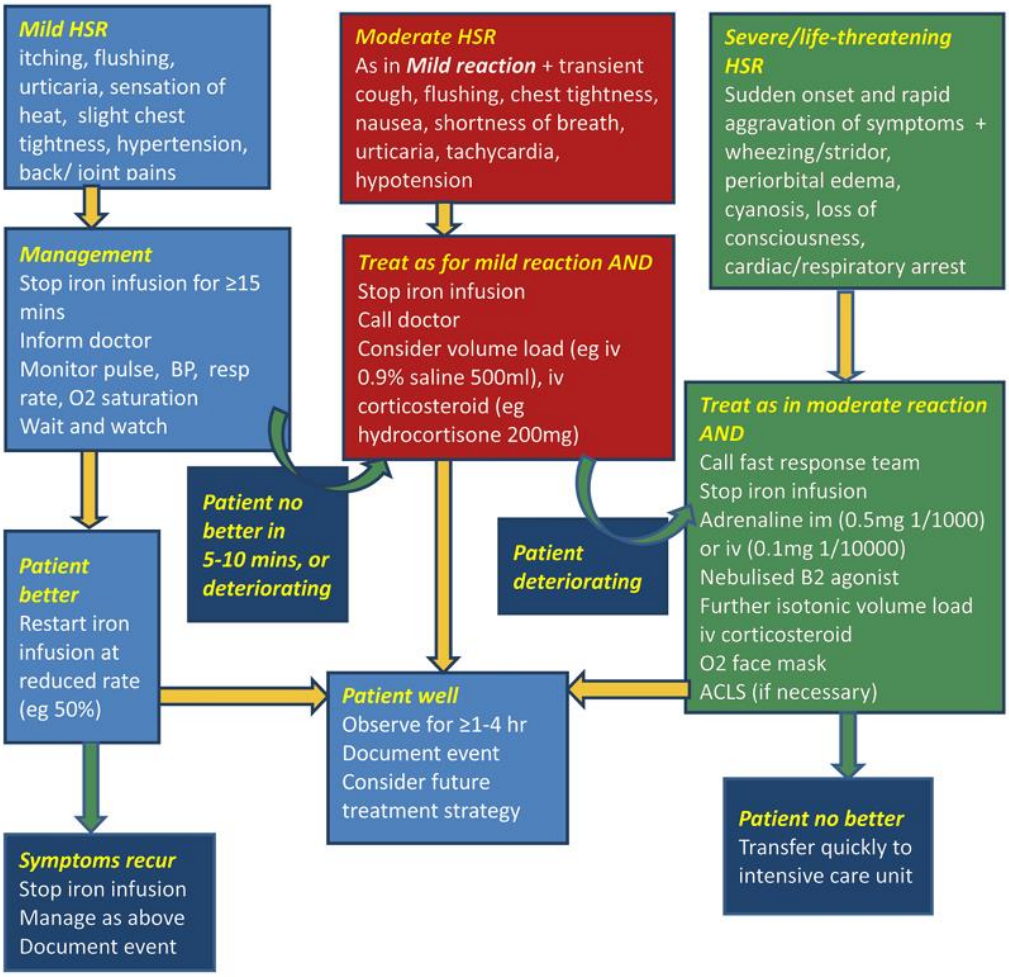
Hydrocortisone – 100 - 500 mg IV to be administered in the case of a moderate allergic reaction which includes: cough, chest tightness, shortness of breath, a rise in heart rate and drop in blood pressure. To administer, the powder should be reconstituted with the included sterile water and pushed through a y port or other injection port over 30 seconds (100 mg) or up to 10 minutes (500 mg). Clinics should have Solu-Cortef (or equivalent) 500 mg on hand when providing iron infusion. The delegating/prescribing provider will provide a prescription for Solu-Cortef annually or as needed for office use for providers delivering IV iron under their delegation in practice.

Epinephrine – epinephrine should only be administered in the case of sever hypersensitivity reactions. Deliver 0.3-0.5 mg (0.3-0.5 mL of 1:1,000 solution) administered intramuscularly into the anterolateral thigh.

Salbutamol – to be administered in moderate to severe hypersensitivity reactions. It can be administered as a nebulizer or as a puffer at a dosage of 2 puffs every 4-6 hours as needed or 2.5 mg nebulizer single dose

Oxygen – Oxygen should be administered in moderate to severe hypersensitivity reactions. Deliver oxygen at a rate greater than 10L/minute initially until O2 sats go above 95% and reduce to minimum flow rate needed to maintain O2 sats above 95%.

Figure 1. Treatment algorithm for IV Iron related hypersensitivity reactions (HSRs)



Managing Tattooing

Tattooing of patients at treatment insertion site due to infiltration of iron infusion is uncommon. Tattooing frequency is estimated at ~1% based on the literature, but data from French pharmacovigilance data indicates in clinical practice it is likely much less frequent. Tattooing is caused by the infiltration of the iron infusion outside of the vessel and staining of the skin near the area of insertion. The severity of tattooing is directly related to the amount of infusate ending up in interstitial space. Some tattooing can be quite severe and will persist for months-years if not treated (See figure 2). In some cases the tattooing can be permanent. The only effective treatment for iron staining of skin is laser therapy and takes between 4-9 treatments at a significant cost to patients. This is a significant concern for patients and results in dissatisfaction.

Figure 2. Iron infusion related skin tattooing

Prevention of iron infusion staining is the most effective way to manage this risk. The following are steps needed for maximal prevention:

- Ensure an appropriate indication for parenteral iron
- Inform the patient of the risk of skin staining at the initial consultation
- Ensure the correct injection site and administration technique is used
- Monitor closely for signs and symptoms of extravasation

When initiating vascular access in iron infusion you should select a large vein in the proximal forearm space (the more distal the access the greater the likelihood for larger more persistent staining). Antecubital access is generally not preferred due to the potential for flexion to disrupt the site and cause infiltration. If using the antecubital fossa or any other flexion point patient should be boarded to prevent flexion.

Access must be done with an angiocatheter and an insertion site adapter. The adapter should be primed with normal saline and vascular access should be confirmed via pulling back on the attached syringe prior to administering iron (See ONIN training video). The access site should be anchored appropriately with both transparent occlusive dressings and other anchoring tape

Patients should be observed throughout their iron infusion treatment more frequently than other infusions to ensure any infiltration that occurs is rapidly managed. They should also be advised to immediately notify staff if they notice: pain, swelling, soreness at the injection site or there is any obvious swelling or discoloration. Should an infiltration occur:

1. Stop the infusion
2. Disconnect the infusion set

3. Take a 10 cc syringe half filled with normal saline and aspirate the rest of fluid from the set attached to the patient if you are using an extension set or other access device like Nexiva™
4. Remove the catheter and apply ice if there is pain at the site or swelling (Cold application will not reduce the spread of staining).
5. Referral for laser therapy

Treatment/Dose Strategies

Intravenous iron therapy can be delivered using one of two types of preparations Iron sucrose (Venofer®) or Iron isomaltoside (Monoferric®). Given the costs, we recommend Venofer as the first choice for patient infusion.

Calculation of total dose of iron in mg to reach target hemoglobin Gazoni Formula:

Total iron need (mg) =
body weight (kg) x [Target hemoglobin-actual hemoglobin (g/dL) x 2.4 + iron stores (mg)

Calculation notes:

1. Use ideal body weight for obese patients (i.e. BMI above 30 Kg/m2); In Pregnancy, use pre-pregnancy weight or ideal body weight if obese prior to pregnancy.
2. Target Hgb is 15 g/dL but a lower value may be used based on clinical judgement. For pregnant and patients with CKD target Hgb (11 g/dL)
3. The iron stores vary from 500 mg to 1000 or use 10 to 15 mg iron/kg body weight, if weight is 35 Kg or less

Intravenous iron dose calculation table

	Recommended Total Iron Sucrose Dose (mg)						
	Desired Hgb Change (g/dL) = Target Hgb – current Hgb						
Body weight	1	2	3	4	5	6	7
40	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1300 mg
45	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1400 mg
50	600 mg	700 mg	900 mg	1000 mg	1100 mg	1200 mg	1500 mg
55	600 mg	800 mg	900 mg	1000 mg	1200 mg	1300 mg	1600 mg
60	600 mg	800 mg	900 mg	1100 mg	1200 mg	1400 mg	1700 mg
65	700 mg	800 mg	1000 mg	1100 mg	1300 mg	1400 mg	1700 mg
70	700 mg	800 mg	1000 mg	1200 mg	1300 mg	1500 mg	1800 mg
75	700 mg	900 mg	1000 mg	1200 mg	1400 mg	1600 mg	1900 mg
80	700 mg	900 mg	1100 mg	1300 mg	1500 mg	1700 mg	2000 mg
85	700 mg	900 mg	1100 mg	1300 mg	1500 mg	1700 mg	2100 mg
90	700 mg	900 mg	1100 mg	1400 mg	1600 mg	1800 mg	2200 mg
95	700 mg	1000 mg	1200 mg	1400 mg	1600 mg	1900 mg	2300 mg
100	700 mg	1000 mg	1200 mg	1500 mg	1700 mg	1900 mg	2400 mg

Per Treatment Dosing Iron Sucrose (Venofer)

- Maximum single dose of iron sucrose to be given at a time in Non-dialysis CKD patients is 500 mg but with limited experience.
- Maximum single dose of iron sucrose in all other patients is 300 mg every week.
- Maximum total cumulative iron sucrose dose administered in 14 days is 1000 mg elemental iron.

Venofer is to be administered diluted with 0.9% sodium chloride at concentrations of 1-2mg/mL over minimum of 15 minutes for each 100 mg. Doses 300 mg or over it should be diluted in 250mL 0.9% sodium chloride.

Per Treatment Dosing Iron Isomaltoside (Monoferric)

- The maximum single dose 20 mg/Kg or 1500 mg whichever is lower. If the total cumulative dose exceeds these limits, divide in 2 doses by administering the maximum allowable dose in the 1st administration, if feasible, and administer the 2 doses at least one week apart

Pre-treatment Evaluation

All patients should be assessed for the following to establish iron deficiency and determine dosing prior to iron infusion treatments:

- CBC with differential
- Serum ferritin
- Iron, transferrin
- Transferrin saturation
- Total iron binding capacity

Summary of lab changes in iron deficiency situations

Lab Test	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Severe iron deficiency with severe anemia
Hgb	Normal range*	Normal range*	90 to 120 g/L	60 to 70 g/L
RBCs size and appearance	Normal	Normal	Normal or slight Hypochromia (↓ MCHC)	Microcytosis £ (↓ MCV) & Hypochromia (↓MCHC)
Serum ferritin ¥	Normal 40 to 200 mcg/L	↓ ¶ Less than 40 mcg/L	↓↓ Less than 20 mcg/L	↓↓↓ Less than 10 mcg/L
Serum iron ≠€	Normal	Normal	↓ Less than 10.7 umol/L	↓↓ Less than 7.1 umol/L
Total Iron-binding capacity (TIBC); transferrin	Normal (53.7 to 64.4 umol/L)	Normal (53.7 to 69.8 umol/L)	↑ (62.6 to 71.6 umol/L)	↑↑ (greater than 73.4 umol/L)
Transferrin saturation (TSAT) €	20 to 50%	20%	↓ Less than 20 %	↓↓ Less than 10%
Reticulocyte Hgb	Normal	Normal	↓	Data not available
Bone marrow iron stain	Adequate iron present	Iron absent		
Erythrocyte zinc protophyrin	Normal	Normal	↑	↑↑

Adopted from UpToDate: Causes and diagnosis of iron deficiency. Available at Link. Accessed on Jan 4th 2021.

Iron deficiency versus anemia of chronic disease

LAB TEST	LAB TEST RESULTS IN			
	IDA	ACD	ACD + IDA	IDA during pregnancy
Hgb	↓ Less than 120 g/L			1st trimester : < 110 g/L 2nd and 3rd trimester : < 105 g/L
Serum ferritin	↓	↑	↓ or normal	↓ or borderline
Serum iron	↓	↓	↓	↓
TIBC	↑	↓	↓ or normal	↑ in 2nd and 3rd trimester
TSAT	↓ < 20%	↓ or normal < 24% in CKD	↓ < 20%	↓ < 20%

Standard Dose Escalation Strategy

Treatment of a patient without established tolerance to intravenous iron should be done at 50% dosage delivered over 50% speed until tolerance is established.

Treatments are to be administered weekly or less frequent as directed. Treatments

Dose reduce 25-50% in cases of reduced leukocytes, RBCs/Hb or elevated transaminases.

Monitoring During Treatment

Iron status should be monitored after treatment course of planned iron repletion is completed. Parameters to be included are:

- CBC with differential
- Serum ferritin
- Iron, transferrin
- Transferrin saturation
- Total iron binding capacity

References

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