Guidance and Approach to Potential Side Effects including Hypersensitivity to IV Iron: *The Nursing Perspective*

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Learning Objectives

• Explain evaluation of iron deficiency anemia and labs to guide effective management of patient outcomes
• Evaluate five IV iron preparations, dosing and administration
• Describe risks and benefits of IV iron therapy to patients that are receiving therapy
Iron – Fast Facts

• Iron is critical for normal hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and synthesis of DNA and various enzymatic processes.

• The total body iron content of an adult ranges from 2 to 4 grams. Approximately 2/3 is in hemoglobin and 1/3 in reticuloendothelial storage and ferritin.

• Most persons typically consume 10-30 mg of iron per day, but will only absorb about 1-2 mg unless iron deficiency is present.

• Iron is lost through skin, hair, intestinal cells, menses, pregnancy (avg 1 gm required/baby)....or bleeding, surgery, hospitalization.

• 1 mg of iron = 1 mL of RBC.
Prevalence of Anemia and Iron Deficiency

• Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide
  – 17% of adults over the age of 65 have iron deficiency

• IDA affects a significant portion of the population with
  – Chronic Kidney Disease
  – Genitourinary Disorders
  – Gastrointestinal Disorders
  – Pre-surgical patients (Ortho, General, Gyn, CV/Thoracic)
  – Up to 40% of critically ill patients

• Recognition and Management of Iron Deficiency Anemia is Critical for all Nurses to Understand
Laboratory Evaluation of Iron Deficiency Anemia and Monitoring
Laboratory Evaluation of Anemia

• Hemoglobin, hematocrit and red cell count
  – World Health Organization guidelines for “anemia”
    • Hgb < 13.0 g/dl for males (usually Hct <39%)
    • Hgb < 12.0 g/dl for females (Usually Hct <36%)

• **MCV**: Mean Corpuscular Volume (normal range 80-100 femtoliters)
  – MCV often < 80 fl in iron deficiency anemia
  – IDA may be normocytic (80-100 fl) under some circumstances

• **RDW** – RBC distribution width (normal range 11.5-14.5%)
  • RDW often increased with Iron Deficiency Anemia
Laboratory Evaluation of Anemia – Beyond Beyond the CBC

• Labs to evaluate iron status:
  – Ferritin
    • Ferritin is an intracellular protein that stores iron and releases it in a controlled fashion
    • Reflects the adequacy of iron stores in normal individuals
    • MOST labs use a lower limit of 12-20 ng/mL for females and 30-45 ng/ml for males; considered by many experts as low
    • KDOQI guidelines for anemia management in chronic kidney disease (CKD) target ferritin > 200 ng/ml in hemodialysis dependent CKD patient and >100 ng/ml in non-dialysis CKD
Laboratory Evaluation of Anemia – Beyond the CBC

• Ferritin (cont’d)
  – Acute phase reactant - often markedly increased in acute illness regardless of iron status, so increased ferritin does not rule out iron deficiency
  – Low ferritin is best single laboratory indicator of iron depletion, but a normal or elevated ferritin does NOT rule out iron deficiency
Laboratory Evaluation of Anemia - Beyond the CBC

- Serum iron
  - Reference range 50 – 150 µg/dL
  - Decreased in iron deficiency and anemia of acute or chronic inflammation
  - Serum iron alone is unreliable due to considerable physiologic variation in results – values may vary 10-40% in an individual within a single day or day-to-day
    - Diurnal variation with highest levels in the morning
Laboratory Evaluation of Anemia - Beyond the CBC

- Total Iron Binding Capacity (TIBC)
  - Total Iron Binding Capacity (TIBC) is an indirect measure of transferrin concentration and is often used interchangeably with transferrin (The principal plasma protein for transport of iron)
    - TIBC expressed in µg/dL (Reference range: 200-400 µg/dL)
    - Increased in iron depletion states
    - Decreased in inflammatory states including anemia of inflammation, malnutrition, liver disease, malignancy
Laboratory Evaluation of Anemia - Beyond the CBC

- Transferrin saturation (TSAT)
  - Percent saturation reflects iron available for erythropoiesis
  - TSAT is usually reported as percent saturation (100 x serum iron/ TIBC)
    - Reference range: 20-45% saturation
  - < 20% consistent with iron deficiency or functional iron deficiency
    - KDOQI guidelines target TSAT >20% in CKD
  - > 45% suggests iron overload
    - Transient increase above 45% typical with I.V. iron Rx
Functional Iron Deficiency

• Chronic or acutely ill patients often have *functional iron deficiency* (FID) despite normal or increased ferritin
  – Include:
    • Post-operative and trauma patients
    • Patients with Inflammatory Bowel Disease, Rheumatoid Arthritis and related diseases, or other chronic inflammatory process
    • Critically ill patients
  • Patients with FID:
    – Are characterized by low iron, low iron binding capacity, and low transferrin saturation
    – May have normal or increased ferritin
Functional Iron Deficiency – Iron Absorption and Availability

• If there is inflammation:
  – Ferritin may be increased
  – Transferrin saturation will be decreased
  – Enteric iron absorption is significantly impaired
  – Release of iron from storage is significantly impaired
  – Erythroid (and other) cells will be deprived of adequate iron and become functionally iron deficient
  – Anemia results
    • FID is the most common cause of “anemia of chronic disease”
Evaluating IDA and Anemia of Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Fe Deficiency Anemia (IDA)</th>
<th>Anemia of Inflammation (AoI)</th>
<th>IDA + AoI</th>
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<tbody>
<tr>
<td>Serum iron</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
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<tr>
<td>Transferrin (TIBC)</td>
<td>Increased</td>
<td>Decreased to normal</td>
<td>Decreased</td>
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<tr>
<td>Transferrin saturation</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
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<tr>
<td>Ferritin</td>
<td>Decreased</td>
<td>Normal to Increased</td>
<td>Decreased to normal</td>
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<tr>
<td>Soluble transferrin receptor</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Soluble transferrin receptor/ferritin index</td>
<td>High (&gt;2)</td>
<td>Low (&lt;1)</td>
<td>High (&gt;2)</td>
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<tr>
<td>Hepcidin</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
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<tr>
<td>CRP</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
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Management of Iron Deficiency: Benefits and Risks of Parenteral Iron Therapy
Enteric Iron

- Lower cost, but slower response
  - Maximum daily iron absorption about 5-7 mg
- 30-40% of patients have gastrointestinal intolerance
  - Constipation, Diarrhea, Gastric Cramping
  - Metallic Taste
  - Leads to significant non-compliance
- Poor absorption in many patients even if tolerated
  - H2-blockers, PPI’s, diet, atrophic gastritis, intestinal malabsorption
- Ineffective in inflammatory states
Emerging Use of IV Iron

- The use of IV iron in the United States has increased significantly over the past decade.
- IV iron use for NON-Renal (CKD, ESRD) indications has driven much of this increase. Examples:
  - Presurgical Anemia Management
  - GI disorders (celiac, Crohns, Peptic Ulcer, etc)
  - OB/GYN – (menorrhagia, pregnancy)
  - Post-op acute blood loss anemia
  - Cancer/ chemotherapy related anemia
IV Iron – Perception versus Reality?

• Most nurses reviewing this presentation were probably taught that intravenous (IV) iron is dangerous
  – The perception of risk is fueled by:
    • Misinterpretation and misinformation of the clinical nature of minor infusion reactions
    • Inappropriate or unnecessary use of premedication
    • Inferences made about the relative safety of the available formulations by regulatory agencies
• Early preparations were associated with a higher rate of serious adverse events, most notably anaphylactic shock
• Newer formulations are much safer with serious adverse events documented as extremely rare
General Nursing Principles – IV Iron

• A well educated and experienced nurse will optimize prevention/management of adverse events and prevent panic for the patient/staff
  – Evidence based use of IV iron and recognizing reactions (mild to severe)
  – How to recognize/manage FISHBANE reactions vs true anaphylaxis (InFeD)

• Patient Education is also extremely important
  – Tell patients to eat and hydrate well before coming
  – Give them an expectation of possible mild AE, like metallic taste and muscle ache – will help manage anxiety levels
  – Explain that severe reactions are rare, that they will be monitored closely, and staff is prepared to treat them if an unexpected event should ever occur

• Calm, well-educated Nurse = calm, well-prepared Patient = less stress for Everybody
Options for IV Iron Replacement

- Formulations available in U.S. include:
  - Low molecular weight iron dextran (InFeD)
  - Sodium Ferric gluconate (Ferrlecit)
  - Iron sucrose (Venofer)
  - Ferumoxytol (Feraheme)
  - Ferric Carboxymaltose (Injectafer)
Low Molecular Weight Iron Dextran (InFeD)

- **Indications:** For treating iron deficiency that is not amenable to oral iron therapy - Allows FDA-approved treatment of a wide range of IDA

- **Dosing:** Provides flexibility in dosing based on the patients needs (e.g. current Hgb, desired Hgb). A “total dose infusion” is commonly utilized for complete iron repletion and should be dosed with pharmacy guidance (up to 1,500 mg/infusion)

- **Administration:**
  - A test dose should be administered prior to the first therapeutic dose, followed by the full therapeutic dose if no signs or symptoms of anaphylactic-type reactions are seen
  - Patients should be observed for signs or symptoms of anaphylactic-type reactions during all INFeD administrations
Low Molecular Weight Iron Dextran (InFeD)

- **Safety profile of iron dextran (InFeD)**
- *Iron Dextran has been associated with life threatening reactions; however, after analysis it has been reported that the majority of these events were related to iron dextran formulations other than Low Molecular Weight Iron Dextran (InFeD)*
  - INFeD is the only low-molecular-weight iron dextran.
  - The FDA has not approved any therapeutically equivalent products to INFeD and therefore it should not be substituted for other forms of Iron Dextran.
Professor Steven Fishbane, described a self-limited reaction consisting of acute chest and back tightness, WITHOUT accompanying hypotension, wheezing, stridor, or periorbital edema, usually after the test dose.

This occurs infrequently, and rarely occurs with re-challenge.

Observation without intervention for approximately five minutes results in the cessation of symptoms.

It is important not to overreact to these minor adverse events as intervention with antihistamines and pressors may cause severe hemodynamic adverse events unrelated to the IV iron.

These events are more likely to occur in patients with an allergic diathesis.

Pretreatment with corticosteroids may be beneficial in patients with an allergic diathesis or in preventing a recurrence of this otherwise minor reaction.
Sodium Ferric Gluconate (Ferrlecit)

- **Indication**
  - Ferrlecit is an intravenous (IV) iron replacement product for the treatment of iron deficiency anemia in patients 6 years and older with chronic kidney disease receiving chronic hemodialysis (HD) and supplemental epoetin therapy

- **Dosing**
  - 1 g repletion therapy with Ferrlecit
  - Recommended dosage is 125 mg of Ferrlecit
    - Can be completed over 8 sequential dialysis treatment sessions
  - The maximum dosage recommended is 125 mg per dose

- **Administration**
  - No test dose required
  - Safe administration as an IV push (12.5 mg/min) or by IV infusion over 1 hour (diluted in 100 mL of 0.9% sodium chloride)
Iron Sucrose (Venofer)

- **Indication**
  - Venofer® is indicated for the treatment of iron deficiency anemia in adult and pediatric patients 2 years and older with chronic kidney disease

- **Dosing and Administration** - No test dose required

<table>
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<tr>
<th>Population</th>
<th>Dose</th>
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<tr>
<td>Adult patients</td>
<td>100 mg slow intravenous injection or infusion</td>
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<tr>
<td>Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD) (2.1)</td>
<td>200 mg slow intravenous injection or infusion</td>
</tr>
<tr>
<td>Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD) (2.2)</td>
<td>300 mg or 400 mg intravenous infusion</td>
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<tr>
<td>Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD) (2.3)</td>
<td>0.5 mg/kg slow intravenous injection or infusion</td>
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<tr>
<td>Pediatric patients</td>
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Ferumoxytol (Feraheme)

• **Indication**
  – Feraheme is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD)

• **Dosing**
  – The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later

• **Administration**
  – No test dose require
  – Each dose infused over at least 15 minutes while the patient is in a reclined or semi-reclined position
Ferric Carboxymaltose (Injectafer)

• **Indication**
  – Injectafer® is an iron replacement product indicated for the treatment of IDA in adult patients:
    • Who have intolerance to oral iron or have had unsatisfactory response to oral iron (e.g. heavy uterine bleeding, postpartum, GI disorders, post-gastric bypass, cancer, heart failure)
    • Who have non-dialysis dependent chronic kidney disease

• **Dosing**
  – Provides up to 1500 mg of iron in just two administrations of up to 750 mg, separated by at least 7 days

• **Administration options**
  – Administer intravenously by IV infusion over at least 15 minutes
  – Slow IV push over at least 7.5 minutes
IV Iron Preparations – Package Insert

Overview of Safety Profile

• Safety Profile
  – Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving IV iron preparations
  – The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope
  – Monitor patients for signs and symptoms of hypersensitivity during and after IV iron administration for at least 30 minutes and until clinically stable following completion of the infusion
  – Only administer IV iron when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions
Adverse Events and IV Iron Therapy

- FDA MedWatch reports (2001-2003) show HMWID was associated with a 3.4-fold increase in odds of life-threatening AEs.
- This analysis likely overestimates AEs with LMWID (all AEs reported by generic name only where attributed to LMWID).
- In tens of thousands of patients in prospective studies SAEs with IV iron are rare.

Practical Matters – IV Iron Selection

• Provider preference may differ amongst specialists
• Hospital formulary may dictate availability (familiarize yourself)
  – Cost may play a role
  – In-patient vs. Out-patient IV iron availability (reimbursement vs cost)
• Adverse Event Rates
  – While there is a similar adverse event rate amongst the IV iron solutions, previous misconceptions may factor into hospital formulary decisions
• Patient Populations
  – Dialysis – Nephrologists may use small doses with each dialysis (Ferrlecit, Venofer)
  – Pregnancy - Venofer and Ferrlecit are category B in pregnancy and others are Category C so some may prefer to use these products in pregnancy
Practical Matters – IV Iron Selection

• Dosing
  – Although it may depend on clinical circumstances (Dialysis vs Pre-Surgical), many generally do not use products with lower dose limits for total dose iron replacement
  – InFed and Injectafer can be used for TDI up to 1500 mg and Feraheme up to 1020 mg; may be desirable in the following circumstances
    • Complete iron repletion is desired (≥ 1,000 mg)
    • Limited time to replete iron and increase Hgb levels (pre-surgical, transfusion avoidance with low Hgb)
    • Patient geography (distance from hospital), mobility issues, or transportation challenge
  – Otherwise choice should depend on patient convenience and chair time
When Treating with IV iron

- For patients with iron deficiency, expect increase in hemoglobin of 0.5 – 1.0 g/dL/week (or more)
  - Assumes adequate marrow reserve and erythropoietic “drive”
- Always evaluate patient for possible sources of chronic blood loss if true iron deficiency
- Many clinicians recommend adding 1 mg oral folate daily and 500 mg Vitamin C twice daily
  - Some data suggests improved bioavailability of administered iron by favoring pathway that keeps iron as ferritin rather than hemosiderin
Summary - Safety of IV Iron

• Pre-medication is often discouraged in the literature (although regularly utilized in some hospitals)
• Most common reactions include allergic (flushing, pruritis, urticaria, rash) and hypotension
  – Hypotension usually associated with rapid infusion
• **Few serious adverse drug events**
  – Overall ADE rate reported as 3.8 per million doses (100 mg = dose)
  – Life-threatening ADEs appear to be more common with HMW iron dextran
• Although serious adverse events are rare patients must be monitored closely during infusion and for at least 30 minutes after treatment
Concluding Thoughts

• Like all treatments, IV iron has benefits and risks which must be reviewed individually; serious adverse events are considered rare
  – Benefits:
    • Prevention/management of anemia (improve quality of life, prevent serious complications associated with anemia)
    • Avoidance of transfusion and the complications associated with exposure to allogeneic blood
  – Risks:
    • More common – allergic reactions, hypotension
    • Rare – dyspnea, chest pain, anaphylactic reactions
• Nursing must be aware of the benefits/risks of IV iron products they administer and carefully monitor patients receiving this treatment
References

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- InFeD [package insert]. Morristown, NJ: Watson Pharma; 2009
- https://www.kidney.org/professionals/guidelines