THE PATHCARE NEWS

IRON DEFICIENCY ANAEMIA IN ADULTS

Introduction
Iron is an intriguing nutrient with many paradoxical characteristics. It is the most abundant element on our planet and yet it is hard for living organisms to access due to its very low solubility. Its ability to switch easily between the ferric and ferrous state is key to its usefulness in many biological reactions. Iron is an essential and usually highly beneficial nutrient, but at the same time can wreak havoc if not appropriately chaperoned to prevent it from causing oxidant damage. These chaperone processes are also critical in with-holding iron from bacterial pathogens and maintaining relatively hypoferric conditions such that microorganisms will not be able to multiply rapidly and can be dealt with by the immune system.

Iron deficiency anaemia (IDA) arises when the balance of iron intake, iron stores, and the body's loss of iron are insufficient to fully support normal physiological functions. Iron deficiency anaemia rarely causes death, but the impact on human health is significant. In the developed world, this disease is easily identified and treated, but frequently overlooked by physicians. Iron deficiency anaemia remains one of the most common, albeit non-fatal diseases, encountered by doctors in the private and public sectors, at all levels of healthcare and across all different medical disciplines.

The diagnosis of IDA (especially in adult men and postmenopausal females) serves as a red flag that could lead to the recognition of a more serious disease, for example the discovery of cancer of the gastrointestinal tract through endoscopic examination.

For many years, nutritional interest in iron focused on its role in haemoglobin formation and oxygen transport but the importance of functional impairments other than haemoglobin synthesis are increasingly recognised. Even mild to moderate forms of iron deficiency can be associated with functional impairments affecting cognitive development, immunity mechanisms and work capacity. IDA in pregnancy is associated with a variety of adverse outcomes for both mother and infant, including risks of sepsis, maternal mortality, perinatal mortality and low birth weight. IDA also reduce learning ability and is associated with increased rates of morbidity.

The discovery of hepcidin (the master regulator of iron homeostasis) has led to a better understanding of the anaemia of chronic disease/inflammation. Pharmaceutical companies are investing considerable resources in the potential therapeutic applications that could be derived from manipulating hepcidin.

THE DIAGNOSIS OF IRON DEFICIENCY ANAEMIA IN ADULTS

Clinical manifestations:
Symptoms: usually primarily due to the anaemia. The same symptoms may also be present in those with reduced iron stores who are not yet anaemic. Typical symptoms include: fatigue, weakness, headache, irritability, exercise intolerance, exertional dyspnoea, vertigo and even angina pectoris. Some of these symptoms are only recognized in retrospect. Pica and pagophagia (pica for ice), restless legs syndrome and hearing loss are some of the more interesting associations with IDA but it is not specific for the disease.

The physical examination: may be normal or may reveal one or more of the following findings: pallor, dry or rough skin, blue sclerae, atrophic glossitis with loss of tongue papillae, angular cheilitis, koilonychia (spoon nails) and alopecia in severe cases. Patients with more severe anaemia may have tachycardia, cardiac murmur or rarely hemodynamic instability.

Laboratory diagnosis:
Iron deficiency and eventually IDA develop in stages and can be assessed by measuring various biochemical indices. Laboratory measurements are essential for the proper diagnosis of iron deficiency. They are most informative when multiple measures of iron status are examined and evaluated in the context of nutritional and medical history. In the vast majority of patients, iron studies should be obtained. The results help to distinguish IDA from other hypochromic microcytic anaemias, document the severity of the deficiency and provide a baseline prior to initiating iron administration.

The FBC and peripheral blood smear:
• The FBC shows a hypochromic microcytic anaemia often with thrombocytosis.
• Low red cell count with increased RDW (which equates to anisocytosis seen on microscopy of the smear)
• The morphology of the smear shows: Pencil cells/cigar cells/elliptocytes, target cells and some teardrop cells.

Serum Ferritin:
Serum ferritin accurately reflects bone marrow iron stores in the absence of an active inflammatory process or chronic disease. Ferritin is an acute phase reactant, and its serum level increases in liver disease, heart failure, infection, inflammation, malignancy, regular alcohol intake, obesity and the metabolic syndrome. Thus, a very low ferritin level (<15ng/mL) is diagnostic of IDA, but a higher ferritin level may be “falsely normal” and cannot be used to eliminate the possibility of iron deficiency in patients with comorbidities. The sensitivity for iron deficiency increases as the cut-off is raised, but specificity decreases. The ideal value is not clear and different cut-off values for serum ferritin are used in different patient populations. A ferritin below 15ng/mL is considered diagnostic of iron deficiency regardless of the patients underlying condition. However, this ferritin cut-off will miss a large proportion of patients with iron deficiency.

Serum Iron:
Serum iron can fluctuate due to dietary intake as well as diurnal variation. By itself, low serum iron is not diagnostic of any condition but must be evaluated in the light of other tests such as transferrin saturation and ferritin. As serum iron may be transiently affected by absorption of iron, it is recommended that the sample be drawn after an overnight fast.
**Serum Transferrin:**

Transferrin is a circulating transport protein for iron. It is increased in iron deficiency but can be decreased in anaemia of chronic disease. Transferrin can also be reported as TIBC. The transferrin concentration can be converted to the TIBC.

**Total iron binding capacity (TIBC)/Transferrin saturation:**

Transferrin saturation (TSAT) is the ratio of serum iron to transferrin/TIBC. Serum iron and TIBC/transferrin saturation are unreliable indicators because of biological variation which occurs as a result of diurnal variation, the presence of infection or inflammatory conditions and recent dietary intake. In addition, transferrin is affected by nutritional status.

**Soluble serum Transferrin receptor (sTfR):**

Level of sTfR is directly proportional to the total amount of cell surface associated transferrin receptor and thus reflects both the quantity of erythroid precursors and the cell surface expression of the receptor per cell. Levels are increased in IDA and anemia associated with ineffective erythropoiesis (myelodysplastic syndrome, megaloblastic anaemia, thalassemia) whilst remaining normal in anaemia of chronic disease. Clinical studies indicate that the sTfR is less affected by inflammation than serum Ferritin.

The incorporation of sTfR into the sTfR-ferritin index (sTfR/log10ferritin) has shown more promise in distinguishing IDA from anaemia of chronic inflammation than sTfR alone. Patients with ACD are likely to have a sTfR-ferritin index <1, whereas those with isolated IDA or IDA with ACD are likely to have a sTfR –ferritin index >2. While commercially available, sTfR lacks standardization and is not widely available.

### Table 1 Stages of iron deficiency

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Iron depletion</th>
<th>Iron-restricted erythropoiesis</th>
<th>Iron deficiency anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow iron stores</td>
<td>+++</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Marrow sideroblasts</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Ferritin (µg/L)*</td>
<td>−40-200</td>
<td>−20</td>
<td>−10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>MCV</td>
<td>Normal</td>
<td>Normal</td>
<td>Slight microcytosis</td>
<td>Microcytic</td>
</tr>
<tr>
<td>Anemia</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal-mildly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Fe (µg/dL), depends on diet</td>
<td>−60-150</td>
<td>−&lt;40</td>
<td>−&lt;20</td>
<td>−&lt;10</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>20-50</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Erythrocyte zinc protoporphyrin (ng/mL)</td>
<td>−30-70</td>
<td>−30-70</td>
<td>−100</td>
<td>−100-200</td>
</tr>
</tbody>
</table>

Fe = iron; MCV = mean corpuscular volume; TIBC = total iron-binding capacity.

*These values represent pure iron deficiency uncomplicated by inflammatory diseases.

**Additional studies can support a diagnosis of IDA in situations in which serum Ferritin is equivocal:**

The biomarkers of hypochromia provide information about the iron supply and are reliable markers of iron restricted erythropoiesis in complex clinical situations. These new red blood cell parameters reported by modern analyzers are exclusive of each manufacturer. Examples of these biomarkers of hypochromia include percentage hypochromic cells and reticulocyte haemoglobin content. These biomarkers are mostly used in the setting of chronic renal failure and hemodialysis and have been incorporated into practise guidelines.

Many individuals with iron deficiency or IDA in resource rich settings do not have the classical presentation of anaemia, either because they come to medical attention before severe deficiency develops or because they have multifactorial anaemia. These patients may require additional assessment with sTfR-ferritin index, repeat testing after treatment of the underlying inflammatory condition, after a therapeutic trial of iron or very rarely, a bone marrow evaluation.

**In summary:** The diagnosis of IDA can be made with any one of the following findings in the appropriate clinical setting.

1. Serum Ferritin <15ng/mL (or <30 ng/mL in a pregnant woman)
2. Serum ferritin <41 ng/mL in a patient with anaemia and comorbidities
3. Transferrin saturation <16% (<20% in patients with inflammatory conditions)
4. Absence of stainable iron in the bone marrow

It is important to keep in mind that iron tests are highly volatile in elderly patients with comorbidities. In addition, the concept of inflamming (first described by Franceschi et al in 2000) describes the low grade pro-inflammatory state associated with the aging process and immunosenescence. There is currently no age specific serum ferritin cut off values to improve the diagnosis of IDA in the elderly population.

**The diagnosis of IDA in chronic kidney disease**

Iron deficiency is the most common reversible cause of anaemia among patients with chronic kidney disease. Patients may have either absolute or functional iron deficiency. Absolute iron deficiency is defined by severely reduced or absent storage iron in bone marrow, liver and spleen. Functional iron deficiency is characterized by adequate iron stores (defined by stainable iron in the bone marrow) but insufficient iron availability for incorporation into erythroid precursors (also called iron restricted erythropoiesis). Among CKD patients, particularly those on hemodialysis, functional iron deficiency is related in part to the administration of erythroid stimulating agents (ESAs), which causes an erythropoietic rate that exceeds the release of iron into the circulation, and to the anaemia of chronic disease/inflammation.

Laboratory criteria used to define iron deficiency and provide indication for treatment are markedly different among CKD patients compared with patients with normal renal function.

**A. Absolute iron deficiency:**

1. Transferrin saturation (TSAT) is < 20%
2. Serum Ferritin <100ng/mL amongst predialysis and peritoneal dialysis patients and <200ng/mL amongst hemodialysis patients.
3. % hypochromic red blood cells > 6%
4. Reticulocyte haemoglobin content (CHR) < 29pg

**B. Functional iron deficiency:**

1. Serum ferritin 100-500 ng/mL and the TSAT 20-30%
Faecal Calprotectin

Chronic abdominal pain with constipation or diarrhoea is a common presenting complaint. It remains challenging for 

INVESTIGATION OF THE UNDERLYING CAUSE OF IRON DEFICIENCY

The major causes of iron deficiency are decreased dietary intake, reduced absorption and blood loss. The diagnostic work up should focus on the likely pathology expected in a specific patient. In the majority of patients the diagnosis and underlying cause of IDA is straightforward. The major cause of IDA in resource rich settings is blood loss, either overt or occult. Overt bleeding is obvious and not difficult for the clinician to recognize, often by history alone. Other causes of blood loss may be overlooked and include: frequent blood donation, excessive diagnostic blood testing, underestimating the degree of menorrhagia, lactation, occult GIT bleeding, intravascular hemolysis with urinary losses (including Paroxysmal Nocturnal Hemoglobinuria, prosthetic heart valves and intensive athletic training), idiopathic pulmonary hemosiderosis, hereditary hemorrhagic telangiectasia and unexpected gastrointestinal parasites. It is especially important to aggressively seek the cause of occult blood loss in adult males and postmenopausal women.

Reduced absorption of iron is an uncommon cause of IDA, especially in healthy individuals in resource rich settings. The most clinically important disorders that affect the mucosal cells responsible for iron absorption are Celiac disease, atrophic/autoimmune gastritis, Helicobacter Pylori infection and bariatric surgery. Inherited disorders that interfere with iron absorption are very rare.

For patients whose IDA remains unexplained or refractory despite standard diagnostic work up, serological or biochemical screening for Celiac disease with anti-endomysial or antigliadin antibodies, for atrophic gastritis with gastrin and anti-parietal cell antibody testing, and for Helicobacter Pylori with IgG antibodies or fecal antigen followed by confirmatory breath testing, is indicated. Cases of suspected Celiac disease should be confirmed with duodenal biopsy. In patients with iron refractory or iron independent anaemia of unknown cause with confirmed H. Pylori infection, eradication of the infection with standard therapy is reported to be curative and thus should be considered.

The definition of refractory IDA is not standardized. One definition is a failure to achieve 1g/DL increase in hemoglobin after 4-6 weeks of at least 100mg of elemental iron therapy/day. Iron refractory iron deficiency anaemia (IRIDA) is a rare inherited disorder in which absorption of oral iron is markedly impaired. IRIDA is caused by loss of function mutations of the TMPRSS6/matriptase 2 gene. Loss of TMPRSS6 function causes iron deficiency due to inappropriate high hepcidin levels, with markedly reduced iron absorption and increased sequestration of iron in macrophages. Patients usually present in childhood with mild hypochromic microcytic anaemia, with low serum iron and transferrin saturation levels. Serum ferritin are mostly in the normal range. The diagnosis is pursued after elimination of other causes if iron deficiency due to malabsorption or anaemia of chronic disease. The diagnosis can be confirmed by genetic testing for the mutation.

THE TREATMENT OF IRON DEFICIENCY ANAEMIA IN ADULTS

Regardless of the presence of symptoms, all patients with IDA and most patients with iron deficiency without anaemia should be treated. The benefit of iron replacement for iron deficiency without anaemia has been demonstrated. An exception is when iron depletion is used therapeutically (porphyria cutanea tarda, polycythemia vera). When treatment is indicated the usual approach is repletion of iron. The approach to therapy is individualised according to etiology and severity of iron deficiency. Blood transfusion should not be used unless the individual has severe symptomatic anaemia or is hemodynamically unstable.

The treatment of IDA includes addressing the underlying cause of the iron deficiency and replacing the iron deficit. Upfront it is useful to calculate the patient’s approximate iron deficit quantitatively. This includes the amount of iron required to normalize the haemoglobin plus the amount required to replete iron stores. The Ganzoni equation:

Total iron deficit = weight (kg) x (target Hb – actual Hb g/L) x 2.4 + iron stores (mg)

Total body iron stores in adult men 10mg/kg and 5mg/kg in women. This quantity should be considered in the context of intestinal iron absorption when considering the likelihood of replacing the deficit by oral administration (constitution secondary to oral iron replacement can be dose limiting in some patients) or to define the amount of parenteral iron to administer.

Oral iron supplementation is the preferred replacement route in most uncomplicated cases of IDA. Oral iron salts are a safe first line treatment for IDA. There is no evidence to suggest that a particular oral preparation is more effective or better tolerated than another if given in equal doses. The use of enteric coated or sustained release capsules are not advised due to the iron being released too far distally in the GIT. The typical replacement dose of elemental iron in adults is 100-200mg/day. However, the best way to administer oral iron is an area of active study, with increasing evidence suggesting that alternate day dosing may result in better iron absorption than daily dosing and may even improve the patients tolerance to treatment. Nausea, vomiting, epigastric discomfort, diarrhea and constipation are common dose-dependent side effects of iron salts. Patients should be alerted that iron might turn their stools a darker colour. Oral iron salts are absorbed best on an empty stomach but are better tolerated when taken with food. Ascorbic acid can facilitate iron absorption, but its addition to the replacement regimen is not clearly cost effective and may increase the adverse effects of iron replacement therapy. An alternative approach is to

<table>
<thead>
<tr>
<th>Table 2 Causes of Iron Deficiency</th>
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<tbody>
<tr>
<td><strong>Blood loss</strong></td>
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<tr>
<td>Hookworm infections</td>
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<tr>
<td>Gastrointestinal disorders (esophageal varices, hemorrhoids, peptic ulcer disease, malignancy)</td>
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<tr>
<td>Menstruation</td>
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<tr>
<td>Pulmonary (hemoptysis, pulmonary hemosiderosis), urologic, or nasal disorders</td>
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<td>Repeated blood donations or clinical blood draws or factitious blood removal</td>
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<tr>
<td>Dialysis</td>
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<tr>
<td>Intravascular hemolysis with hemoglobinuria (paroxysmal nocturnal hemoglobinuria, prosthetic heart valve)</td>
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<tr>
<td><strong>Increased iron requirements</strong></td>
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<tr>
<td>Rapid growth during infancy and adolescence</td>
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<tr>
<td>Erythropoietin therapy</td>
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<tr>
<td>Pregnancy and lactation</td>
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<tr>
<td><strong>Inadequate iron supply</strong></td>
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<tr>
<td>Poor dietary intake (generally not an independent cause in adults)</td>
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<tr>
<td>Malabsorption</td>
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<tr>
<td>Duodenum and upper jejunum diseases (celiac disease, gastric bypass surgery, inflammatory bowel disease)</td>
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<tr>
<td>Achlorhydria</td>
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<tr>
<td>Autoimmune atrophic gastritis/ Helicobacter pylori colonization</td>
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<tr>
<td>Congenital disorders of iron transport (iron-refractory iron deficiency anemia, hereditary hypotransferrinemia, divalent metal transporter 1 disease)</td>
</tr>
</tbody>
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References:
1. NICEdiagnostics guidance 11. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel.
instruct patients to take oral iron supplements with orange juice. Antacids, the tannins found in tea, calcium supplements, bran and whole grains, if taken concurrently with iron supplements, can all decrease iron absorption. Iron should be given 2 hours before or 4 hours after ingestion of antacids. Treatment with oral iron should continue for at least 3 months after the haemoglobin normalizes to replete iron stores.

Oral heme iron polypeptide (HIP/Proferin), derived through the proteolytic digestion of porcine/bovine haemoglobin is another available oral iron formulation. Heme-iron is more efficiently absorbed and via a different mechanism than elemental iron. Further studies are warranted to determine whether HIP is more efficacious and/or better tolerated than other oral iron formulations. It is currently more expensive than oral iron salts.

The safety of IV iron preparations are much improved. Low molecular weight iron dextran (Cosmofer) have been found to be much safer. The availability of IV iron formulations with improved toxicity profiles has lowered the threshold at which many patients would consider switching from an oral to an IV preparation. The corollary of this is that all clinicians administering IV iron should have adequate personnel, training and equipment to manage extremely rare but potentially life-threatening adverse events, including medications to treat anaphylaxis, resuscitation equipment and provisions for intensive care management.

True allergic reactions are exceedingly rare and vastly overestimated, largely due to previous historical experiences with HMW iron dextran. Routine premedication is not advised. For individuals with asthma, inflammatory rheumatic conditions or multiple drug allergies, limited premedication (glucocorticoid alone) is given. In contrast to serious allergic reactions, IV iron may be associated with non-allergic infusion reactions including self-limiting urticanial, palpitations, dizziness and neck and back spasm. Generally these occur in <1% of individuals and do not progress to more serious reactions.

In addition, patients with a history of inflammatory arthritis (eg, Rheumatoid Arthritis) commonly experience a flare of arthritis during IV iron infusion, which is usually well controlled with glucocorticoid premedication and a brief course of glucocorticoids (3-4 days) following the infusion.

The distinction between rate related infusion reactions and allergic reactions may be challenging and a detailed discussion regarding this, an approach to reduce the risks as well as the management of allergic and infusion reactions is beyond the scope of this article.

Parenteral iron should be given intravenously (intramuscular is painful) and is indicated where:

1. Absolute noncompliance with or intolerance to oral iron therapy
2. Ongoing blood loss that exceeds the capacity of oral iron to meet needs.
3. Proven intestinal malabsorption. (due to use of antacids, active inflammatory bowel syndrome)
4. Gastrointestinal/bariatric surgery
5. Chronic renal failure (dialysis and non-dialysis)
6. Anaemia due to malignancy treated with erythropoiesis stimulating agents (ESA)
7. Iron deficiency that does not respond to oral iron therapy due to concomitant inflammatory states. (elevated hepcidin reduce iron absorption)

The use of IV iron allows administration of nearly full replacement doses in 1-2 infusions, depending on the product. The frequency of serious adverse events is comparable among products and therefore not a consideration when choosing among products. Considerations when choosing a product include: cost, how rapid infusion may be given and number of doses required. For patients with a reaction to an IV product, many experts would switch to a different IV iron product.

Iron sucrose (Venofer) and iron gluconate (Ferricite) have very low incidences of anaphylaxis (no fatal cases of anaphylaxis has been reported) and their administration does not require a test dose. Side effects of iron sucrose and iron gluconate include mild arthralgia and myalgia. Disadvantages of these newer formulations include greater cost and the inability to give a total replacement dose in a single infusion because they cause GI and vaso-active reactions at doses > 200-400mg. Newer iron preparations have been developed to enable more rapid high dose bolus injections. These include Ferumoxytol (Feraheme) and Ferric carboxymaltose (FCM/Injectafer/Ferinject). Ferumoxytol can cause brighter signal on MRI and if an MRI is planned within 3 months of administration, the radiologist should be notified. Initial experience with FCM raised concerns about hypophosphatemia observed following administration. Subsequently only rare reports of clinical sequelae related to hypophosphatemia have been reported. Serum phosphate levels may need to be monitored in selected populations such as those with borderline phosphate levels at baseline.

IDA patients receiving supplemental iron generally respond with a reticulocytosis within 7-10 days of starting treatment. A haemoglobin response generally occurs within 2 weeks but may take 6-8 weeks to fully correct, and a serum ferritin should correct once additional iron (beyond that to correct the haemoglobin) accumulates to replete body stores. The failure to respond to oral iron should prompt consideration of ongoing bleeding, poor patient compliance, poor iron absorption, inadequate replacement dosing, more than one diagnosis or appropriateness of the diagnosis.

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References:
1. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. SL Schrier. 2018. Up to date.com

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