Iron Deficiency: What Are the Future Trends in Diagnostics and Therapeutics?

Moderator: Carlo Brugnara*
Experts: John Adamson, Michael Auerbach, Robert Kane, Iain Macdougall, and Alan Mast

A review of currently available diagnostic and therapeutic modalities for the laboratory assessment of iron deficiencies has identified a need for novel markers to complement the traditional serum iron, ferritin, and transferrin measurements and to improve the assessment of the best therapeutic options for treating these disorders. Newer markers, such as serum transferrin receptor and reticulocyte hemoglobin (Hb) content, have not ended up being integrated into clinical practice. This experience thus provides a cautionary tale about the translation of promising research findings into clinical practice. Measurements of serum hepcidin appear to be promising and worth pursuing in larger diagnostic and therapeutic trials. When intravenous (IV) iron replacement therapy is indicated, the availability of several different preparations can present challenges in selecting the most appropriate agent and in assessing their risk/benefit ratios. The relative safety of IV iron preparations needs assessment by prospective, blinded, controlled trials. In this Q&A article, leading experts in the field of diagnosis and treatment of iron-deficient states present their opinions on the advantages and disadvantages of current and future laboratory assessments of iron deficiencies and the therapeutic options currently available to treat these conditions.

In a majority of patients, iron deficiency is identified with simple and traditional hematological and biochemical markers that have remained essentially unchanged for decades. Is there a need to add any other biomarker for the diagnosis of nutritional iron deficiency or iron deficiency due to blood loss? From your perspective, what are the requirements for ideal biomarker(s) for monitoring individualized therapy with iron and erythropoiesis-stimulating agents, especially as applied to anemia of chronic disease and chronic kidney disease (CKD) patients treated with dialysis?

John Adamson: This is a very complex question. I don’t look for biomarkers to try to sort out the various contributors to anemia [iron vs erythropoietin (EPO)]. Nutritional iron deficiency, however it is defined, is still iron deficiency and needs treatment. I often encounter patients who have inflammation as well as suspected iron deficiency. Rather than rely on a single test, or a battery of tests, I give the patient parenteral iron (to avoid issues of compliance or absorption) to remove whatever contribution iron deficiency might be making to the anemia. Whatever anemia remains is due to something other than real iron deficiency.

Iain Macdougall: Ever since EPO therapy joined the therapeutic arena for treating chronic anemia in dialysis patients over 20 years ago, nephrologists recognized the problem of concomitant iron deficiency, not only absolute but also functional iron deficiency. We rapidly realized that...
the traditional markers of iron status such as serum ferritin and transferrin saturation had limitations, and we have been striving to find a more sensitive biomarker since. The requirements for this ideal biomarker would be that it is readily available and can reliably predict an Hb response to IV iron therapy. We thought that measurement of serum hepcidin might turn out to satisfy this need, but the preliminary data have not been as encouraging as we had previously hoped.

Alan Mast: Ferritin is a very good test for identifying iron deficiency from poor nutrition or blood loss in otherwise healthy patients. It has been available for several decades now, and there has not been a new test, or a combination of tests, developed that improves on the diagnostic utility of ferritin alone in these patients. The problem with ferritin is that it is an acute-phase reactant, and its diagnostic utility falls in patients with underlying diseases. An ideal biomarker would have perfect sensitivity and specificity for predicting the availability of iron for new red blood cell synthesis in patients receiving EPO, regardless of the underlying disease. In this regard, reticulocyte Hb content is a relatively good marker of iron available for red blood cell synthesis over the previous 4 days and can be helpful for individualizing IV iron therapy in patients receiving EPO.

Robert Kane: Identifying uncomplicated iron deficiency due to inadequate intake, poor absorption, or excess iron loss (hemorrhage) is straightforward with a good clinical history including details of diet, prior gastroduodenal surgery (including gastric banding), pica, stool character (think celiac disease), and the traditional measures of iron saturation and ferritin. Dyspepsia may suggest bleeding or the use of proton-pump inhibitors, which can impair iron absorption. When chronic disease conditions coexist with iron deficiency, the iron saturation and ferritin are usually unreliable for distinguishing iron deficiency; assessing iron stores in the marrow and/or a modest dose of parenteral iron as a therapeutic trial can be considered. Also, with comorbidities, circulating Hb responses to iron replacement are blunted, Hb will not usually reach the reference interval, and the expectation of therapy should not be to achieve a normal Hb concentration.

Anemia management of patients with CKD on dialysis is a constant challenge, since a chronic disease state coexists with ongoing procedural blood loss, reduced marrow erythroid response, restricted availability of storage iron to reenter the erythron pool, shortened red cell survival, and possibly other factors. For many years, EPO prescribing information empirically endorsed an Hb target of 10–12 g/dL for all patients, without direct clinical evidence to support this target range and without adequate safety information derived from rigorous controlled trials. Current EPO drug-prescribing information expresses the goal of an individualized approach, using EPO as necessary to minimize the need for red cell transfusion support for each patient. Controlled trials have shown that EPO cannot eliminate the need for some transfusions. Current therapy for dialysis patients involves balancing EPO and iron supplementation to minimize transfusion use while simultaneously attempting to minimize the risk of strokes, heart attacks, and death associated with EPO therapy. Hb is a poor surrogate for guiding EPO therapy, due to the wide fluctuations in Hb concentrations usually encountered. EPO measurements have not been found to be useful in guiding EPO therapy in CKD. Whether EPO measurements could help to minimize EPO dosing has not been studied. Despite adequate iron stores and serum iron values, giving an additional IV iron infusion to patients with CKD may produce a small increment in Hb. This approach incurs the risk of excess tissue iron and organ toxicity at some point. There is no available biomarker to guide this strategy.

What do you think are the reasons for the limited use of new markers, such as soluble transferrin receptor (sTfR) and reticulocyte Hb content?

John Adamson: The tests have simply not added much to our diagnostic abilities, except in very restricted situations. And even then I am not sure. Even with a “positive” serum sTfR test, the proof is in the response of the patient to iron replacement. As for the reticulocyte Hb content, not all laboratories have the technology to generate the result, and if the local nephrology community (i.e., the major dialysis chains in the US) has not embraced the test, then it is unlikely that most American nephrologists, other than a few cognoscenti, will make much out of it. Also, as I understand it, the test does not differentiate iron-restricted erythropoiesis due to inflammation from iron-restricted erythropoi-
esis due to inadequate (slow) release of iron from stores under the drive of pharmacologically stimulated erythropoiesis.

**Iain Macdougall:** In the renal setting, for patients receiving EPO therapy, the sTfR is unfortunately unreliable, since it responds not only to iron deficiency but also to increased erythropoietic activity. Unless the patient is in steady state on EPO, the sTfR has little to offer. Other markers, such as reticulocyte Hb content and percentage of hypochromic red cells, have been shown to be of value but have traditionally not been accessible to many nephrologists, since these tests were peculiar to one particular brand of analyzers. However, this is changing, with similar technologies now being adopted by most modern-day blood count analyzers. To date, however, there are limited data on the usefulness and validity of these newer parameters in renal patients.

**Alan Mast:** sTfR is very sensitive for iron deficiency and is not an acute-phase reactant. Therefore, it can be useful in diagnosing and treating iron deficiency in patients with an underlying inflammatory disease, such as rheumatoid arthritis, where ferritin is increased. However, it is not a specific test for iron deficiency. It is also increased in conditions that have increased red blood cell synthesis, such as hemolytic anemia and sickle cell anemia. I think ferritin’s lack of specificity for iron deficiency has limited its use. Reticulocyte Hb content is also a very sensitive test for iron-deficient erythropoiesis. Currently, it is available and automatically performed during the reticulocyte analyses on Siemens and Sysmex hematology analyzers, but not on those made by other manufacturers. Clinical laboratories could report reticulocyte Hb content at no additional cost with each reticulocyte analysis performed, but it seems that they rarely do. I think that it has limited use, primarily because of lack of awareness of its availability and education about when it is clinically useful.

**What do you think are the possible uses of hepcidin and some of the more recently discovered biomarkers for iron metabolism?**

**John Adamson:** Hepcidin, as a drug, would be most helpful in the treatment of patients with hereditary forms of iron overload. It remains to be seen whether drugs that interfere with hepcidin would be of use in patients with the anemia of inflammation. For that very small group of patients with iron-refractory iron deficiency anemia, an antihepcidin drug should prove to be very helpful. However, the real problem lies in the nature of the drug. If it is antibody-based therapy, however well-meaning, it may have costs beyond benefits and potentially lead to other complications, such as acquired resistance.

**Iain Macdougall:** There have now been quite a number of papers reporting measurement of serum hepcidin in renal patients. Measurement of urinary hepcidin is useless in these individuals, owing to their kidney failure. Several reports looking at serum hepcidin as a predictor of a response to IV iron therapy have emerged, as was shown for the percentage of hypochromic red cells several years ago. The main study comes from an Italian group, but this study unfortunately showed poor sensitivities and specificities for hepcidin and also confirmed the value of hypochromic red cells in detecting functional iron deficiency. The other big problem with measurement of serum hepcidin is its intrapatient variability, as we and others have shown.

**Alan Mast:** Hepcidin is a relatively recently discovered hormone produced by the liver that regulates the absorption of iron from the gastrointestinal (GI) tract and release of iron from macrophages and hepatic stores. Although it is an acute-phase reactant and tends to correlate with ferritin, the correlation is not perfect. Ferritin is a specific measure of iron stores. Although hepcidin production is regulated by iron stores, it is also regulated by the rate of erythropoiesis and by the presence or absence of sufficient iron physiologically available for new red blood cell synthesis. Thus, it may be clinically useful in diagnosis of some types of anemia where ferritin is not. In addition to its potential use in diagnosis of anemia, hepcidin is also likely to be diagnostically useful in patients with iron-overload syndromes. Numerous clinical studies are now being conducted to further define the clinical utility for hepcidin in a variety of diseases.

**Should one consider using IV iron in conditions that have been traditionally treated with oral iron supplements, such as anemia of pregnancy or chronic inflammatory bowel disease? Should the threshold for the use of IV iron be lowered, considering the increased safety of the new preparations?**

**John Adamson:** In my opinion, IV iron absolutely should be considered, and certainly for inflammatory bowel syndrome, where you might have a combination of poor absorption and excessive loss. I believe that we underestimate the degree of noncompliance with oral iron therapy, particularly considering that the drug is most effective when given multiple times a day and on an empty stomach. The availability of multiple parenteral iron preparations with very good safety profiles has transformed the way I treat even the most straightforward cases of iron deficiency. That said, mine is a
referral practice, and so primary care physicians should always consider oral iron supplementation in straightforward cases. As for pregnancy, I would try to manage with oral iron, but I know that there are efforts to move parenteral iron preparations to the approval stage for pregnancy. However, the “anemia of pregnancy” is not due just to iron deficiency, and each patient must be addressed as an individual.

Michael Auerbach: The answer is a resounding “Yes!” Estimates are that up to 70% of patients to whom oral iron is prescribed are nonadherent. In patients with inflammatory bowel disease, where oral iron is associated with severe side effects, is poorly absorbed, has limited efficacy, and worsens bowel symptoms, IV iron is efficacious and extremely well tolerated with no to marginal toxicity. In pregnant patients, constipation is a common problem, owing to increased progesterone, often worsened by prenatal vitamins; oral iron is usually associated with worsening constipation, less often with diarrhea or gastric discomfort. IV iron has routinely been shown in published series to be effective and safe. In women with menorrhagia, oral iron cannot keep up with the ongoing losses, whereas IV iron has consistently been found in prospective studies to be more efficacious and better tolerated. This applies to a host of other conditions where ongoing losses exceed absorptive capacity. We have shown the safety and efficacy of complete-replacement dosing using 1000 mg of low molecular weight iron dextran administered as a 1-h infusion in a host of conditions associated with iron lack. Published evidence supports a larger and earlier role of IV iron.

Iain Macdougall: Potentially, yes. There is now a large body of evidence that suggests that GI symptoms are considerably less with IV iron, compared to oral iron preparations, and the modern-day IV irons are very much safer than their predecessors. However, we still need reassurance about the long-term safety of IV iron, particularly with regard to its potential for increasing susceptibility to infections and enhancing oxidative stress.

Robert Kane: Most chronic GI conditions, from gastrectomy to inflammatory bowel disease to celiac disease, are better managed with IV iron rather than oral iron, due to the much reduced GI toxicity with IV iron, as well as being able to bypass all of the issues with variable absorption (and intake!) of oral iron. Also, periodically giving a single large dose of IV iron can achieve substantial iron repletion efficiently. Current evidence is not available for choosing a particular IV iron product based on safety, since no direct comparisons of products have been performed and, overall, the serious risks are uncommon.

Use of IV iron in pregnancy poses a special challenge. Many pregnant women are anemic. Some are iron deficient, and this can usually be affirmed by the standard laboratory tests for iron saturation and ferritin. Many pregnant women cannot add the GI distress of oral iron on top of their existing GI distress. IV iron is almost universally successful in addressing the iron needs of pregnancy. Efficacy is not the question. However, the risk, even remote, of an anaphylactic reaction to IV iron is daunting in this population. Perhaps if there were compelling evidence of substantial benefits of IV iron repletion (vs oral iron supplementation) given during pregnancy on measurable outcomes postpartum for the child or mother, the risk-to-benefit assessment could tip toward more-regular use of IV iron. Perhaps there is a degree of iron deficiency anemia that is so severe that IV iron is routinely justified in pregnancy. Strong evidence on which to judge comparative safety is not available.

How can one optimize the selection of the most appropriate IV iron preparation for a specific patient and disease among those now available in the US and European markets?

John Adamson: All parenteral iron preparations are considered equal in terms of their ability to repair iron deficiency and restore iron stores. I personally don’t think that the indication drives the decision about which preparation to use. There is considerable controversy about the relative safety profiles of the various preparations, especially the iron dextrans. As of this moment, these are the preparations that carry a “black box” warning in the US. The selection of the preparation often is determined by the setting of delivery. Some medical centers/large office practices are comfortable with rapid iron infusions but not with the longer periods of time recommended for infusion of the iron dextrans, for instance.

Michael Auerbach: The setting in which IV iron is administered influences how to answer this question. In dialysis, the decision as to which iron to use is economic and makes little clinical difference with thrice-weekly visits. However, for all other clinical settings where IV iron is preferred, infusing the total dose (1 g
or more) in a single setting (TDI) is as effective and safe as bolus injections, but less expensive and more convenient according to several prospective clinical trials. Only iron dextran, ferumoxytol (US only), isomaltoside, and carboxymaltose (the latter 2 Europe only) can be given as a TDI in 1 h or less. The 2 salts should not be administered in doses over 250 mg for gluconate and 300 mg for sucrose due to significant infusion reactions, ostensibly due to free iron with the less tightly bound smaller carbohydrate carriers. Of the 2 iron dextrans available, the high molecular weight formulation (Dexferrum) should be used only with caution, based on the preponderance of published data. We recently completed a 60-patient pilot study with ferumoxytol administered as a 1020-mg infusion in 15 min. That no serious adverse events were observed is consistent with published evidence that the remaining products can be administered as a TDI.

Iain Macdougall: This is a difficult one. We need further comparative head-to-head studies of the various IV iron preparations before we can begin to address this issue.

Robert Kane: At present, we do not have an evidence base with which to select a clear winner for efficacy or safety, so choices are made for economy or circumstances. In the dialysis setting, replacing procedural iron losses periodically with any of the approved products is a reasonable option, with product cost often the deciding factor. In CKD on dialysis, the use of IV iron products to drive Hb production in the absence of iron deficiency (so-called functional iron deficiency) needs more study of the longer-term safety, since excess body iron can be expected. For all other iron-deficient patients in need of IV iron, single infusions intended to achieve substantial iron repletion are efficient and appropriate. Product labeling describes an extended infusion process for the iron dextrans and, for the iron sugar products, at least a 30-min observation period following infusion for safety monitoring.

What are the challenges in properly identifying and reporting toxicity and side effects for oral iron and IV iron preparations?

Michael Auerbach: When high molecular weight iron dextran is avoided, serious adverse events are vanishingly rare. In studies encompassing thousands of patients across a host of conditions associated with iron lack, no serious toxicity has been observed. Nonetheless, there exists a folklore suggesting IV iron is dangerous. Premedication with diphenhydramine, which can cause hypotension, somnolence, sweating, and supraventricular tachycardia, is often responsible for reactions attributable to IV iron. Minor infusion reactions, usually consisting of minor arthralgias, myalgias, or flushing, occur infrequently. The absence of hypotension, tachypnea, tachycardia, stridor, wheezing, or periorbital edema excludes a severe adverse event. No intervention is necessary. Measured tryptase levels following these reactions have always been normal. Inappropriate intervention with antihistamines or pressors can convert innocent, self-limited reactions into hemodynamically severe ones, increasing the perception of danger with IV iron. Prospective studies comparing iron sucrose to iron dextran and to ferumoxytol have shown no significant differences in safety profiles. However, after more than 2 decades of standard IV iron use in dialysis patients and increasing use in many other clinical settings, including chemotherapy-induced anemia, this critical adverse-event profile is underappreciated. Current adverse event–reporting systems do not allow comparative safety conclusions. Education clarifying the incidence and clinical nature of adverse events is needed.

Iain Macdougall: We have to be very careful in using pharmacovigilance data for this, and the only robust way to assess this is in the context of properly conducted prospective (preferably randomized controlled) trials.

Robert Kane: The best method to determine comparative safety is a prospective, blinded, controlled trial comparing 2 (or more) products. No such trial has been performed. Manufacturers are rarely enthralled by this opportunity to do a direct comparison. For the IV iron products, since both serious and severe adverse reactions are uncommon, large numbers of patients would be required, informed consent could be challenging (“our purpose is to compare the toxicity . . .”), and equipoise is not common among investigators. The US Food and Drug Administration maintains a registry, the Adverse Event Reporting System (AERS), but the system contains only enumerations (cases reported), and there is no acceptable method to calculate adverse-event rates or to compare them. There is no certainty that the reported event has a causal relationship to the suspect drug; reporting is voluntary and may fluctuate with other publicity about a drug.

The comparative toxicities of various oral iron products are not well documented, since they are not studied the way prescription drugs are tested. Each of us likely has individual treatment preferences honed by years of patient feedback. To reduce intolerance, I generally start patients on 1 tablet daily of a lower-iron-content pill (ferrous gluconate, 35 mg of elemental
iron) taken with food for a few days and then try twice daily. If the stool color is not darkening, the patients are not taking it. Iron absorption is enhanced in the fasting state, while GI tolerance generally is worse! Although GI absorption of iron is enhanced in iron deficiency, I’m not persuaded that achieving a higher GI content of elemental iron with higher-dose iron products is useful or tolerated as well, and many enteric coated products can be identified unchanged in the stool. With some luck and flexibility in trying several products, a balance of tolerance and efficacy can be reached with an oral iron product. For many patients, IV iron administration is preferred.

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