Introduction

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More than 300 years have passed since Sydenham first added iron filings in cold wine to treat the “green sickness” later coined as “chlorosis” by Blaud, who first used ferrous sulfate in 1832. As oral iron is inexpensive, easy to obtain, and effective when tolerated and taken for conditions in which iron replenishment is needed, it remains the current frontline standard. In contrast, oral iron is usually poorly tolerated and, as a result, often ineffective, and occasionally also harmful. High-quality meta-analyses report unacceptable gastrointestinal perturbations in 70–75% of those to whom it is prescribed, which mitigates adherence. In contradistinction, with the advent of newer formulations of intravenous iron with complex carbohydrate cores which bind elemental iron more tightly, limiting release of labile free iron to subclinical levels, it is now possible to administer a complete or near-complete replacement dose in one seamless, convenient, inexpensive, safe, and effective infusion. The possibility of single encounter repletion markedly facilitates care and effectively eliminates nonadherence. It is not the goal of these captivating papers, written by world-renowned experts, to eschew the use of oral iron. Instead, we wish to attract attention to a litany of conditions in which there are high-quality published supportive data placing intravenous iron to the forefront. Virtually everyone reading this special issue will have learned during their medical education that intravenous iron is dangerous. To that, we open our

journey with an erudite review of the safety of oral and intravenous formulations by Tom DeLoughery from the Oregon Health Sciences University. In his incisive and informative review, Dr. DeLoughery leads us through the magnitude of adverse effects of iron deficiency and using published data provides an algorithm for choosing replacement formulations. In doing so, he supplies us with a useful profile of safety and adverse events associated with both routes of administration, while allaying unfounded fears of risks, especially anaphylaxis, with the use of intravenous iron. The reader will also enjoy his concise road map for amelioration of adverse events irrespective of the formulation or route chosen.

In the second paper, George M. Rodgers and Jeffrey A. Gilreath from the University of Utah Health Sciences Center lead us through the role of iron replacement in cancer- and chemotherapy-induced anemia. While this may seem specialized to some, in this well-done and informative paper, the authors take us through a well-organized description of the pathophysiology of iron-restricted erythropoiesis (also known as functional iron deficiency) which most readers will remember as anemia of chronic disease. In their comprehensive review of high-quality published clinical trials of the treatment of anemia in malignancy, the reader will gain an understanding of the relatively newly elucidated role of hepcidin in health and disease, which so dramatically impacts providers’

treatment options. The authors, again using high-quality prospective data from randomized clinical trials, clarify the importance of iron supplementation to synergize with and maximize the performance of the much more expensive erythropoiesis-stimulating agents. To paraphrase their prose, “a more complete understanding of iron metabolism will hopefully lead to the development of novel erythropoietic adjuncts to help ameliorate functional iron deficiency anemia and improve quality of life, without compromising outcome.”

Anemia in the perioperative setting is not only fraught with poor outcomes, not the least of which are increased length of hospital stay, postoperative infections, and increased blood transfusions, which have considerable morbidity and poorer surgical outcomes that are often overlooked. In their excellent review of the causes and management of this all too common problem, Susana Gómez-Ramírez (University Hospital Virgen de la Victoria) and Manuel Munoz (University of Málaga School of Medicine) from Malaga (Spain), collaborating with their colleagues Elvira Bisbe (University Hospital Mar- Esperanza, Barcelona, Spain), Donat R. Spahn (University Hospital of Zurich, Switzerland), and Aryeh Shander from the Englewood Hospital and Medical Center in New Jersey (USA), stress the importance of proactive diagnosis and interventions which dramatically decrease morbidity. In reading this most informative review, readers are likely to be surprised, not only at the magnitude of the problem but also at the formidable improvements which can be enjoyed with a minimal but organized approach to anemia management. The paper contains a useful algorithm to guide the reader to appropriate choices for iron replacement, which helps to improve hospital care and patient outcome while reducing costs and improving resource utilization.

Iron deficiency is a near ubiquitous complication of inflammatory bowel diseases and is the most common extraintestinal manifestation of these disorders. Guidelines for its management differ in the United States, where oral iron remains frontline, and Europe, where the intravenous route is preferred. In their remarkable review of the problem, Kristine M. Jimenez and Christoph Gasche from the Medical University of Vienna (Austria) pave the way for the understanding of the pathophysiology, symptoms, morbidity, and management of anemia in those who suffer from this serious condition. In doing so, they provide high-quality evidence for the proscription of oral iron by reviewing evidence-based clinical trials which inform on its harm. The reader will learn of the direct toxic effects of enteral formulations of iron replacement on the

intestinal epithelium and become familiar with the way oral iron impacts bacterial growth in patients with inflammatory bowel diseases, negatively altering the microbiome in a class of patients so rife with gastrointestinal adverse events. High-quality data supporting the safety and efficacy of intravenous iron are provided. Provocative evidence supporting the role of iron replacement in improving disease activity independent of anemia, as well as a largely unknown and fascinating story of intestinal hypoxia, its interaction with hypoxia-inducible factor, thrombocytosis, and thromboembolism in this thrombophilic population, unfolds.

In the first of 3 manuscripts from the Rabin Medical Center of Tel Aviv University in Petah Tikva (Israel), Anat Gafer-Gvili and Uzi Gafer take us through the relatively unknown saga of the role of iron deficiency after renal transplantation. In a population so rife with comorbidities, the authors, using quality evidence-based medicine from randomized controlled trials, direct a treatment paradigm which can improve quality of life, decrease complications, and, most importantly, decrease mortality. After reading this review, the reader will become familiar with the efficacy and safety of intravenous iron in a population so rife with medical complications.

In the second paper from Petah Tikva, Anat Gafer-Gvili, Amir Schechter, and Benaya Rozen-Zvi review the role of iron deficiency in chronic kidney disease, the disorder in which the foundation for intravenous iron treatment was built. With the advent of the release of recombinant human erythropoietin for anemia in patients with kidney diseases, especially patients on dialysis, it was anticipated that the dispiriting symptoms of severe anemia would be obviated. Yet 4 years after its release, the majority were not being treated to target, with many not being treated at all. Following the revelation by Eschbach and Adamson, intravenous and not oral iron was necessary to synergize and optimize erythropoiesis-stimulating agent therapy. As a result, intravenous iron became standard of care for these patients. The authors review existing data, elucidate the physiology of anemia of kidney disease, and put forth recommendations for the management of this ubiquitous comorbidity. In doing so, they show how the addition of intravenous iron – and not oral iron – added to the treatment paradigm for anemia of chronic kidney diseases improves performance and decreases both the time to reach the target hemoglobin level as well as expensive erythropoiesis-stimulating agents dosing needed to reach the target and concomitantly improves cardiovascular outcome, work capacity, and even survival.

In the final paper, the reader is taken through the new era of iron deficiency treatment accompanying congestive heart failure with intravenous iron treatment. In this review, Oren Zusman, Osnat Itzhaki Ben Zadok, and Anat Gafer-Gvili highlight the role of iron deficiency with and without anemia as an independent prognostic factor in congestive heart failure. After reading this paper, the reader will be astonished by how iron deficiency, overlooked for decades, negatively impacts outcome in patients with congestive heart failure. High-quality supportive data on the safety and efficacy of intravenous iron is reviewed. As a result of these new data, it is likely the European Society of Cardiology Guidelines will strengthen their recommendation, and a new algorithm incorporating intravenous iron for the management of iron deficiency and iron deficiency anemia associated with congestive heart failure will shortly appear.

We hope you will find this compendium exciting, enlightening, and clinically useful. We understand that a

recommendation to overcome 3-century-old therapeutic modalities may be disconcerting at first. However, throughout this issue, recommendations for the use of intravenous iron across a host of conditions associated with iron deficiency are all evidenced based. Compared to oral iron, intravenous iron has far fewer adverse events and less nonadherence, is more effective, and synergizes better with erythropoiesis-stimulating agents resulting in huge cost savings. Unlike oral iron, intravenous iron can overcome the inhibition of erythropoiesis by hepcidin in anemia induced by cancer and cancer chemotherapy, inflammatory bowel diseases, and chronic kidney diseases. With new formulations of intravenous iron that allow for safe and complete replacement of iron in a single infusion over 15–60 min, we believe we have made a compelling argument for its forward move in the treatment of the most prevalent malady on the planet.