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Clinical Review

IDENTIFICATION AND MANAGEMENT OF IRON DEFICIENCY ANEMIA IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Iron deficiency anemia is the most common hematologic disorder in the United States and worldwide. Yet, clinical guidelines for the identification and management of this disorder in the emergency department are lacking. Objective of Review: This clinical review examines strategies for identifying and treating iron deficiency anemia in the emergency department, with a focus on the role of oral iron therapy, intravenous iron therapy, as well as red blood cell transfusion. The article highlights both the available evidence on this topic and the need for future research. Discussion: The diagnosis of iron deficiency anemia has important clinical implications and, although testing is generally straightforward, it may be underrecognized. The scant literature available describing emergency department practice patterns for iron deficiency anemia suggests there is room for improvement. In particular, intravenous iron may be underutilized and red blood cell transfusions administered too liberally. Conclusions: Iron deficiency anemia is common and many patients can be treated effectively with oral iron. For selected patients with moderate-to-severe iron deficiency anemia, intravenous iron is safe and more effective than oral iron. Red blood cell transfusions should be used rarely for hemodynamically stable patients with iron deficiency irrespective of hemoglobin levels.**

☐ **Keywords—iron deficiency anemia; intravenous iron; oral iron; transfusion**

INTRODUCTION

Iron deficiency anemia is the most common hematologic disorder both globally and in the United States (1,2). Despite the frequency with which this disease process is encountered, the prevalence in U.S. emergency departments (EDs) is unknown, and evidence-based guidelines on the management of iron deficiency anemia in this setting are nonexistent. In the absence of such guidelines, there is variability in both the diagnostic evaluation and treatment approach for such patients. For years, oral iron has been advocated as first-line therapy in most patients with iron deficiency anemia, with intravenous iron reserved for patients who have failed oral iron therapy or who are determined to be poor candidates for a variety of reasons. Transfusion of packed red blood cells is often administered based upon arbitrary hemoglobin thresholds or an assessment of symptoms attributed to low hemoglobin concentrations. There is increasing evidence that intravenous iron may be superior to oral iron alone for many patients and, in some circumstances, may be superior to red blood cell transfusion. This article examines current evidence regarding the identification and management of iron deficiency anemia for ED patients.

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DISCUSSION

Prevalence of Iron Deficiency Anemia in the ED

Data on the prevalence of iron deficiency anemia, or anemia in general, among the general ED population is lacking. However, the overall prevalence of anemia in the United States appears to be increasing. National Health and Nutrition Examination Surveys (NHANES) data from 2003 to 2012 demonstrates that the prevalence of anemia increased during this 10-year period from 4% to 7.1%, with moderate-to-severe anemia nearly doubling from 1% to 1.9%. High-risk groups include pregnant women, women of reproductive age, persons of African-American race or Hispanic ethnicity, as well as the elderly (2). Limited data exist for anemia prevalence among pediatric ED patients and women presenting with abnormal uterine bleeding. A cross-sectional study of more than 2000 pediatric patients from an inner-city pediatric ED found an overall anemia prevalence of 14%, with higher percentages among uninsured patients (18.5%) and females of childbearing age (20.7%) (3). A retrospective study of women presenting to a U.S. ED with abnormal uterine bleeding found an anemia prevalence of 35%, although the presence of iron deficiency was not specifically reported (4). Studies defining the prevalence of iron deficiency anemia in the general U.S. ED population and among specific patient groups in the ED are needed.

Identifying Iron Deficiency Anemia in the ED

Iron deficiency can occur with or without anemia. Identifying iron deficiency without anemia does have important implications for patients and further outpatient workup and treatment would be indicated to prevent progression to anemia. However, for the purposes of the ED provider, we will focus on identifying iron deficiency as the etiology of anemia.

The World Health Organization defines anemia as hemoglobin < 13 g/dL in men, < 12 g/dL in non-pregnant women, and < 11 g/dL in pregnancy. Moderate and severe anemia are defined as hemoglobin < 11 g/dL and < 8 g/dL, respectively, in men and non-pregnant women, and < 10 g/dL and < 7 g/dL, respectively, if pregnant (5). Although the clinical history may strongly suggest iron deficiency as the etiology of anemia, laboratory evaluation is required for definitive diagnosis. Low iron stores and hypochromic microcytic erythrocytes are the hallmark of iron deficiency anemia. Therefore, laboratory evaluation includes a complete blood count with red blood cell indices and serum measurements of iron, transferrin saturation, total iron binding capacity, and ferritin.

Red blood cell indices typically demonstrate a low mean corpuscular volume (MCV), low mean corpuscular hemoglobin concentration, low red blood cell count, and elevation of the red cell distribution width (RDW). Importantly, a normal MCV does not exclude the presence of iron deficiency and a low MCV alone is not diagnostic of iron deficiency (6). A serum ferritin level is the most sensitive and specific indicator of iron deficiency anemia. When using a cutoff value < 30 μg/L, the sensitivity and specificity are 92% and 98%, respectively (7,8). However, as serum ferritin is an acute-phase reactant, a normal or elevated ferritin level cannot exclude iron deficiency. Higher thresholds for ferritin may be considered in inflammatory disease states. A serum ferritin threshold of < 100 μg/L has been proposed for patients with chronic kidney disease, inflammatory bowel disease, and congestive heart failure (9). A transferrin saturation may be particularly helpful in scenarios with equivocal ferritin levels, as a value of < 20% strongly implies absolute or functional iron deficiency. Measurement of the soluble transferrin receptor may be considered in cases where the diagnosis remains unclear, despite standard investigations, such as when the anemia is multifactorial in origin, as in patients with mixed iron deficiency anemia and anemia of chronic inflammation (6).

While studies of iron metabolism may be extremely helpful in the diagnostic evaluation of iron deficiency anemia, they may not be absolutely necessary to guide initial treatment in the ED. For instance, in an otherwise healthy young woman presenting for evaluation of abnormal uterine bleeding, a complete blood count demonstrating hypochromic microcytic anemia, increased RDW and low red blood cell count would be highly suggestive of iron deficiency anemia, and iron supplementation would be indicated. In one of the only studies examining the prevalence of iron deficiency in the general ED population, authors at a hospital in Ontario, Canada proposed an algorithm to identify and treat ED patients with iron deficiency anemia. In the proposed algorithm, anemia combined with either low ferritin or MCV < 75 fL, in patients with a previously normal MCV, could be used to aid clinicians in the diagnosis and treatment of iron deficiency (10). Figure 1 represents a simple modified algorithm for ED diagnosis of iron deficiency anemia.

Treatment of Iron Deficiency Anemia in the ED

The source of iron deficiency in the majority of adult patients evaluated in U.S. EDs is likely to be chronic blood loss from gynecologic or gastrointestinal bleeding. However, patients being evaluated for acute blood loss anemia associated with hemodynamic instability require resuscitation and hemorrhage control. These patients are

excluded from this review, which is focused on the identification and management of the hemodynamically stable patient with iron deficiency anemia.

In the hemodynamically stable patient with iron deficiency anemia, blood transfusion should be the exception rather than the rule. Most patients with iron deficiency anemia should be treated with iron supplementation and efforts should be made to identify and treat the source of bleeding as soon as feasibly possible. The preferred iron treatment and route of administration will depend on a number of factors, including degree and acuity of anemia, source of blood loss, treatment options for addressing further hemorrhage, comorbid medical conditions, cost, and availability of various iron formulations, as well as patient preference.

Oral Iron

Oral iron is typically considered the first-line treatment, as it is inexpensive, readily available, and generally effective, although it is not without limitations. Oral iron supplements are available in either the ferric (Fe^{+++}) or ferrous (Fe^{++}) form, with the latter used more often due to better absorption. Ferrous iron supplements include ferrous fumarate, sulfate, and gluconate, which vary in the content of absorbable elemental iron, although studies suggest these preparations are roughly equivalent with regard to bioavailability (12). Absorption may be improved by taking iron without food and with supplemental vitamin C.

Oral iron therapy may lead to an increase in reticulocyte count within 1 week and improvement in hemoglobin levels by the second week of therapy (13). Historically, the typical dosing regimen for adults is 100–200 mg of elemental iron per day in divided doses (7). Interestingly, more recent studies in non-anemic patients with iron depletion indicate that lower doses given less frequently (e.g., once daily or every other day) may improve absorption (14–16). The proposed mechanism for improved absorption is related to increased serum hepcidin levels after an initial dose of oral iron, which limits subsequent iron absorption for up to 24 h. If studies demonstrate improved efficacy in iron deficiency anemia patients with a low-dose, alternate-day regimen, this strategy may improve tolerance and adherence to therapy.

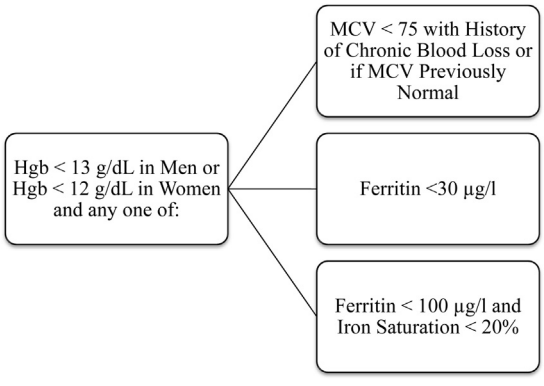

Figure 1. Identification of iron deficiency in the emergency department. Hgb = hemoglobin; MCV = mean corpuscular volume. Adapted from Khadadah et al., with permission (11). Copyright 2016 by Cambridge University Press.

The major barriers to effectiveness of oral iron replacement therapy are the prolonged time course required for adequate repletion, gastrointestinal side effects, and conditions that limit adequate absorption, particularly when ongoing blood loss exists. Oral replacement therapy for several months may be required to adequately replete iron stores. Gastrointestinal side effects with oral iron are very common and may result in non-adherence in up to 50% of patients (17).

Multiple underlying medical and surgical conditions may result in impaired iron absorption, including inflammatory bowel disease, celiac disease, chronic pancreatitis, *Helicobacter pylori* infection, gastrectomy, gastric bypass, and small bowel resection. Furthermore, commonly prescribed medications, such as proton-pump inhibitors and histamine-2 receptor antagonist that suppress gastric acid production can also inhibit iron absorption (18,19). Even when absorption is not impaired, patients with ongoing gastrointestinal or gynecologic bleeding, or other sources of blood loss, may not be able absorb enough enteral iron to keep up with losses. Alternative strategies should be considered when oral iron therapy alone is ineffective or inadequate.

Blood Transfusion

Red blood cell transfusion produces an immediate, transient increase in hemoglobin concentration and delivers approximately 200–250 mg of iron per unit of blood. However, red blood cell transfusion is not a benign intervention and may be overutilized in ED management of iron deficiency anemia. Risks of transfusion are well-documented and include transmission of infectious diseases, transfusion-associated lung injury, transfusion-associated cardiac overload, hemolytic transfusion reactions, and alloimmunization (20,21). Alloimmunization may be a particular concern for women of childbearing potential, as it may increase risk of complications in future pregnancies. Table 1 provides an overview of selected adverse event rates associated with red blood cell transfusion (22–27).

The financial costs of blood transfusion must also be considered. Using an activities-based costing model, Shander et al. estimate that the combined direct and indirect costs of a red blood cell transfusion range from $522

Table 1. Selected Adverse Event Rates with Red Blood Cell Transfusion

Adverse Events	Rate per Transfusion of Red Blood Cells
Infection transmission	
HIV, HBV, HCV	< 1:1,000,000
Bacterial infection (22)	1:5,000,000
Non-infectious transfusion risk	
Life-threatening transfusion reactions* (23)	1:139,908
Death due to hemolysis (23)	1:1,250,000
Transfusion error (24)	1:19,000
Febrile non-hemolytic reactions (25)	1:2000
Mild allergic reactions (26)	1:100
Alloantibody development (27)	1:13

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.
* Reactions requiring major medical intervention, such as vasopressors, intubation, or transfer to an intensive care unit.

to $1183 (mean $761) (28). Red cell transfusion should be administered to patients with severe iron deficiency anemia with associated hemodynamic instability, severe anemia symptoms (e.g., chest pain, dyspnea at rest, syncope), or in select patients for whom significant ongoing blood loss is expected.

A restrictive approach to transfusion has been demonstrated to be at least as effective, if not superior, to liberal transfusion strategies in a variety of clinical settings, including patients with acute upper gastrointestinal hemorrhage and critically ill patients (29,30). In one trial of 521 hemodynamically stable women with severe postpartum anemia (defined as hemoglobin < 8 g/dL), patients were randomized to red cell transfusion or transfusion only for severe symptoms. The group randomized to transfusion only for severe symptoms received significantly less blood (88 vs. 517 units). Significantly, there was no difference between groups in complications or hemoglobin concentration at 6 weeks (31). It stands to reason then that a restrictive strategy—or perhaps more restrictive strategy—would likely apply in non-critically ill patients with chronic or subacute blood loss anemia in the ED.

Although multiple guidelines do support restrictive transfusion thresholds in general, there are no well-supported "transfusion-triggers" for stable patients with iron deficiency anemia. The AABB (formerly known as American Association of Blood Banks), in their recommendations for the *Choosing Wisely* campaign, goes so far as to say that "transfusion is not recommended for iron deficiency or iron deficiency anemia in a hemodynamically stable patient irrespective of his or her hemoglobin level" (32). We believe providers should take this recommendation into consideration, while also considering the unique characteristics and circumstances of individual patients. Transfusions should be used judiciously and only after careful consideration of alternative therapies.

Intravenous Iron

Intravenous iron is an effective and rapid means for treating iron deficiency and provides many potential advantages over both oral iron therapy and blood transfusion. Intravenous iron is the preferred means of iron repletion in patients who have failed oral iron therapy, those with comorbid medical or surgical conditions associated with impaired iron absorption, and in patients for whom ongoing blood losses are expected to exceed absorptive capacity.

Despite a large body of evidence demonstrating safety and superiority over oral iron in many settings, intravenous iron is not commonly used in the ED. Current evidence regarding contemporary ED management of iron deficiency anemia is limited to two studies in a Toronto, Ontario tertiary care ED (10,11). Spradbrow et al performed a retrospective chart audit to describe the characteristics of patients with iron deficiency anemia, the utilization of iron products, and the appropriateness of red cell transfusion based on a novel algorithm developed by the authors (10). In addition to suggesting that nearly half of the patients who received red cell transfusions could have been treated with alternative methods, they also found that only 4% of the patients discharged from the ED received intravenous iron.

There exist many possible reasons for the infrequent use of intravenous iron in the ED. Reasons might include unfamiliarity with intravenous iron, hospital formulary limitations, concerns regarding safety and efficacy as compared to alternative therapies, perceived cost concerns and time constraints, and lack of published clinical guidelines. Safety concerns may be the result of the use of older formulations of intravenous iron that have since been removed from the market, namely high-molecular-weight iron dextran, which was associated with an unacceptable risk of life-threatening allergic reactions. This may have prejudiced providers to avoid intravenous iron in general.

There are currently five formulations of intravenous iron available in the United States. A vast abundance of literature supports the safety of these products and extremely low adverse event rate with these newer formulations (33). Intravenous formulations currently available in the United States include iron sucrose, low-molecular-weight iron dextran (LMWID), sodium ferric gluconate, ferumoxytol, and ferric carboxymaltose. Table 2 provides an overview of intravenous iron preparations available in the United States (34).

Fear of using intravenous iron may stem from concerns of serious allergic reactions, although some have also suggested a potential of increased infection risk.

Table 2. Intravenous Iron Indications, Warnings, Adult Dosing, and Cost

Variable	Ferric Carboxymaltose	Ferumoxytol	Ferric Gluconate	Iron Sucrose	Low-Molecular Weight Iron Dextran
FDA-approved indications	IDA in patients with intolerance to oral iron or an unsatisfactory response to oral iron; or who have non-dialysis dependent CKD	IDA in patients with intolerance to oral iron or an unsatisfactory response to oral iron or who have CKD	IDA in patients with CKD undergoing hemodialysis and receiving epoetin therapy	IDA in patients with CKD	IDA in patients for whom oral iron is unsatisfactory or impossible
Maximum FDA-approved dose	750 mg i.v. over 15 min with a second dose after 7 days*	510 mg i.v. over at least 15 min with a second dose 3–8 days later	125 mg i.v. over 1 h per dialysis session	400 mg i.v. over 2.5 h†	100 mg i.v. over 2 min (1 h after test dose)
Boxed warning for anaphylaxis	No	Yes	No	No	Yes
Test dose required	No	No	No	No	Yes
Non–FDA-approved total dose infusions	1000 mg i.v. over 15 min	1020 mg i.v. over 30 min	NA	NA	1000 mg i.v. over 1 h (25-mg test dose given over first 15 min)
Price per 1000 mg, $‡	1072	969	152	230	273

CKD = chronic kidney disease; FDA = Food and Drug Administration; IDA = iron deficiency anemia.
* Ferric carboxymaltose is approved as a 1000 mg single-dose infusion in Europe.
† Iron sucrose is approved as 200-mg infusion for non-dialysis dependent-chronic kidney disease; 100 mg infusion for hemodialysis-dependent kidney disease; and 300-mg infusion over 1.5 h 14 days apart, followed by one 400-mg infusion over 2.5 h 14 days later for patients with peritoneal dialysis-dependent chronic kidney disease.
‡ Pricing data is based on Medicare Part B Drug Average Sale Pricing from the 2019 ASP Drug Pricing Files (April 2019 Update) (34).

Chertow et al. obtained data from the U.S. Food and Drug Administration (FDA) adverse event reports for four intravenous iron formulations from 2001 to 2003 (including high-molecular weight iron dextran). They found an overall adverse event rate of roughly 38 per million and a death rate of 0.3 per million. The absolute rates of life-threatening adverse events for iron sucrose, sodium ferric gluconate, and LMWID were only 0.6, 0.9, and 3.3 per million, respectively (35). In context, per the U.S. weather service, the risk of dying as a consequence of an iron infusion is far exceeded by the annual risk of being struck by lightning (1 in 1.2 million) (36).

A systematic review and meta-analysis, which included 10,390 patients from 103 randomized trials comparing intravenous iron to another comparator, also assessed the safety of various intravenous iron preparations. Importantly, the five intravenous iron formulations currently available in the United States were represented in these trials. Intravenous iron was associated with an increased risk of infusion reactions. However there was no increased risk of serious adverse events, adverse events requiring discontinuation of therapy or increased risk of infections in patients treated with intravenous iron. Although serious infusion reactions were more common with intravenous iron overall, ferric gluconate was the only individual formulation associated with this increased risk. No anaphylaxis or death due to any intravenous iron formulation was reported in any of the included trials (37).

An iron formulation that could be administered as a single effective dose in a short time frame would be the preferred method of administration in the ED. Of the currently available formulations, single-dose infusions can be administered with LMWID, ferumoxytol, and ferric carboxymaltose (FCM). Other formulations, such as iron sucrose, would require multiple encounters to deliver the dose required to adequately replete iron stores and sufficiently increase hemoglobin levels. Iron isomaltoside, which is available in Europe, can also be given as a single-dose infusion (38).

LMWID is FDA-approved only for a dose of 100 mg per day and also requires a one-time 25-mg test dose prior to full dose administration. However, evidence supports safety and efficacy of much higher doses (38–41). Auerbach et al. reported their experience with 1266 total dose infusions of LMWID in which 1000 mg was safely administered over the course of 1 h, and no patients experienced a serious adverse event. The 25-mg test dose was given over 15 min and remainder of the dose given over 45 min (39).

Ferumoxytol is FDA-approved as a 510-mg dose infusion given over 15 min, with a second dose administered 3–8 days later. In a prospective study of 60 patients with iron deficiency anemia who received ferumoxytol in a

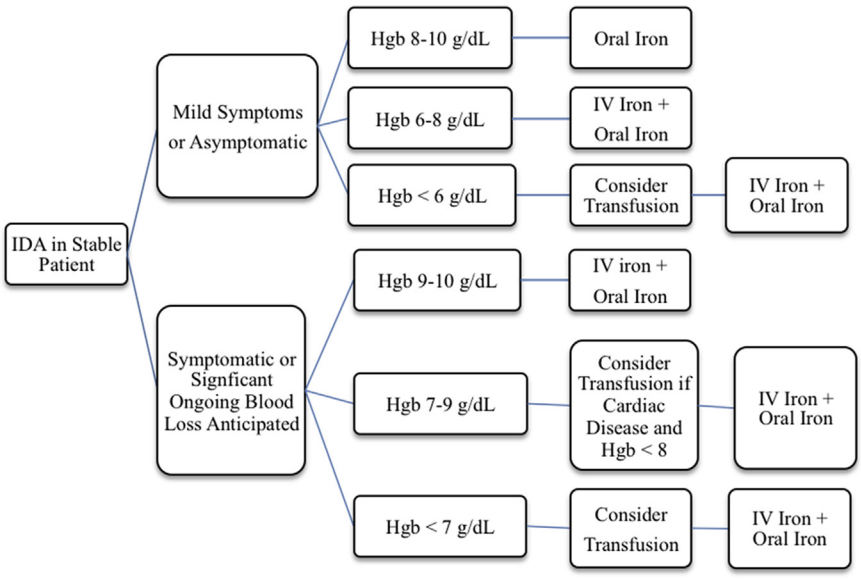

Figure 2. Emergency department management algorithm for stable patients with iron deficiency anemia. Hgb = hemoglobin; IDA = iron deficiency anemia; IV = intravenous. Mild symptoms: fatigue, generalized weakness, exertional dyspnea, or palpitations. Adapted from Khadadah et al., with permission (11). Copyright 2016 by Cambridge University Press.

single 1020-mg dose, there were no serious adverse events; and patients had a mean increase in hemoglobin of 2.1 mg/dL at 4 weeks (42). FCM is approved as a single-dose infusion of 750 mg given over 15 min (and is approved as a 1000-mg infusion in Europe). A large randomized trial of FCM vs. standard medical care in women with postpartum anemia or anemia due to heavy menstrual bleeding found that FCM given as a single dose of up to 1000 mg was safe and more effective than oral iron (43). In a separate randomized trial of 477 women with iron deficiency anemia and abnormal uterine bleeding, 1000 mg of FCM was found to be more effective than oral iron in correcting anemia and improving quality of life measures (44).

Although further studies are needed to best determine the precise role of intravenous iron in the ED, a previously referenced study by Khadadah et al. demonstrated a simple and effective strategy (11). After performing a chart audit of ED management of iron deficiency anemia, the authors engaged their emergency physician colleagues in developing and implementing an algorithm for iron deficiency anemia, which included indications for red cell transfusion, oral iron, and intravenous iron (10). Figure 2 illustrates a similar potential management algorithm adapted with permission. During the ensuing 2 years, intravenous iron use increased from 1 dose in the 3-month audit period to 4.7 uses per month. Red cell transfusion appropriateness increased from 53% to > 90%. Although a relatively small single-center study, the potential benefit of a reduction in transfusions is echoed in a systematic review and meta-analysis of 22 studies with more than 3000 patients in various settings. The results of this analysis indicate that intravenous iron therapy is associated with a significant reduction in the probability of receiving a blood transfusion (45).

Spanish researchers have also described their experience with intravenous iron in a "fast-track anemia clinic" in the ED. ED patients identified as having moderate-to-severe iron deficiency anemia, who did not require immediate transfusion or hospitalization, were referred to the fast-track clinic. If there were no contraindications, patients were treated with intravenous iron (FCM). Red cell transfusion was used only for patients meeting restrictive criteria based upon age, symptoms, and the presence of high-risk cardiopulmonary disease. For example, asymptomatic patients were transfused only for hemoglobin < 5 g/dL and elderly symptomatic patients without high-risk criteria were transfused for hemoglobin < 7 g/dL. The authors demonstrated that this practice was not only clinically effective, but also cost-saving compared to standard practice (46,47). While creating a dedicated ED anemia clinic would not be practical for most EDs, similar protocols could be implemented in the ED or observation unit.

CONCLUSIONS

Although there is a paucity of studies specifically addressing ED prevalence, diagnosis, and treatment of iron deficiency anemia, an abundance of literature exists in other arenas, with findings applicable to emergency medicine. The diagnosis of iron deficiency anemia is generally straightforward and, in many cases, can be made from the history, examination, and simple

laboratory tests commonly available in the ED. Efforts should be made to identify and treat the underlying cause of blood loss or malabsorption in all cases, although the acuity and severity of the anemia will dictate the rapidity and extent of these efforts in the acute setting. Oral iron and outpatient referral may be all that is required for many patients. Red blood cell transfusion is likely overutilized in stable patients with potentially serious consequences and increased costs to the patient and health care system. Future prospective studies are needed to further define the role of intravenous iron therapies in the management of iron deficiency anemia in the ED. Given the abundance of literature supporting safety and efficacy of various parenteral iron formulations, it is likely an underused treatment and may have a role in reducing red cell transfusions and improving ED patient outcomes. Without established clinical guidelines, emergency physicians should continue to do what they do best: apply the best-available evidence to the patient in front of them, consider the risks and benefits of therapeutics, collaborate with colleagues and administrators to improve patient care, and continuously seek opportunities to do better. For iron deficiency anemia, we may be able to do better.

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ARTICLE SUMMARY

1. Why is this topic important?

Iron deficiency anemia (IDA) is the most common hematologic disorder in the United States and worldwide and is a common problem in the emergency department (ED). Guidelines for identification and management of IDA in the ED are non-existent. Red blood cell transfusions may be overutilized, thus exposing patients to unnecessary risk of harm and increased costs. Intravenous iron is infrequently used in the ED, however, it may have a role in reducing red blood cell transfusions and improving patient outcomes.

2. What does this review attempt to show?

This review addresses the evaluation and treatment of iron deficiency anemia in the hemodynamically stable ED patient.

3. What are the key findings?

Iron deficiency anemia may be strongly suspected based upon history and examination findings, though laboratory studies easily obtained in the ED are required for confirmation. Oral iron supplementation is effective for many patients, though is not without significant limitations. Red cell transfusions are likely given too liberally when alternative therapies would be as, or more, effective. The precise role of intravenous iron needs to be further defined in future studies, however, the available literature suggests that intravenous iron is safe and more effective than oral iron for selected patients. Intravenous iron may also reduce the risk of requiring red blood transfusion.

4. How is patient care impacted?

Identification of iron deficiency anemia has important implications for immediate care of patients in the ED and for ongoing outpatient management. Improved awareness of the benefits, limitations, and harms of oral iron, intravenous iron, and blood transfusion will lead to improved patient outcomes.