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Management of iron deficiency anemia: A survey of pediatric hematology/oncology specialists

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Abstract

Background—Iron deficiency anemia (IDA) is the most common hematologic condition in children and adolescents in the United States (US). No prior reports have described the management of IDA by a large cohort of pediatric hematology-oncology specialists.

Procedure—A 20-question electronic survey that solicited responses to two hypothetical cases of IDA was sent to active members of the American Society of Pediatric Hematology/Oncology (ASPHO) in the United States.

Results—Of 1,217 recipients, 398 (32.7%) reported regularly treating IDA and completed the survey. In a toddler with nutritional IDA, 15% (N=61) of respondents reported ordering no diagnostic test beyond a complete blood count. Otherwise, wide variability in laboratory testing was reported. For treatment, most respondents would prescribe ferrous sulfate (N=335, 84%) dosed at 6 mg/kg/day (N=248, 62%) divided twice daily (N=272, 68%). The recommended duration of iron treatment after resolution of anemia and normalized serum ferritin varied widely from 0 months to 3 months. For an adolescent with heavy menstrual bleeding and IDA, most respondents recommended ferrous sulfate (N=327, 83%), with dosing based on the number of tablets daily. For IDA refractory to oral treatment, intravenous iron therapy was recommended most frequently, 48% (N=188) using iron sucrose, 17% (n=68) ferric gluconate, and 15% (N=60) low molecular weight iron dextran.

Conclusion—The approach to diagnosis and treatment of IDA in childhood was widely variable among responding ASPHO members. Given the lack of an evidence base to guide clinical decision making, further research investigating IDA management is needed.

Keywords

iron deficiency anemia; iron therapy

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Conflicts of Interest

Gensavis Pharmaceuticals LLC is funding an investigator initiated clinical trial conducted by the study authors, which compares NovaFerrum[®] to ferrous sulfate for the treatment of nutritional IDA in young children (BESTIRON).

Introduction

Iron deficiency anemia (IDA) affects 3 to 7% of young children and up to 9% of adolescent females in the United States (US).^(1, 2) Young patients with IDA have suboptimal neurodevelopmental outcomes, including lower IQ, decreased visual and auditory processing time and poorer executive functioning. ^(3–5) These deficits are greater for those with more severe and chronic IDA and can persist after correction of the anemia. In addition, young women with IDA due to heavy menstrual bleeding often report fatigue, which may affect school and work performance. Accordingly, emphasis has focused on prevention and early detection of IDA through routine screening. ⁽⁶⁾ Yet, such efforts have been unsuccessful overall as they have not substantially reduced the rate of IDA in the US. ⁽⁷⁾

Evidence-based guidelines for management of IDA are lacking for several reasons. First, the diagnosis of IDA can be challenging in that a test which is both sensitive and specific does not exist. Second, while IDA therapy consists primarily of oral iron supplements, evidence to support a specific treatment approach, including total daily dose of iron, dosing schedule and total duration of treatment, is limited. ⁽⁸⁾ Given lack of rigorous research aimed at improving IDA therapy in patients of all ages, we sought as an initial step to define contemporary self-reported diagnostic and treatment practices employed by pediatric hematology/oncology specialists. These physicians often encounter patients with IDA who present with more severe or persistent disease, many of whom have failed initial attempts with oral iron therapy. We hypothesized that substantial variability would exist among physicians who diagnose and treat IDA. We further aimed to identify physician attributes associated with differences in IDA management.

Methods

We conducted a cross-sectional electronic survey in October 2013 of pediatric hematology/oncology physicians in the US who were active members of the American Society of Pediatric Hematology/Oncology (ASPHO). It consisted of 20 multiple-choice questions and was expected to require no more than 15 minutes to complete. Consent for research participation was implied by survey completion. The Institutional Review Board of the University of the Texas Southwestern Medical Center approved this study.

In addition to requesting demographic information, the survey included two typical IDA case scenarios (full survey instrument is available in Supplemental Appendix I). The first was a healthy 18 month old male referred for outpatient evaluation of anemia with a dietary history consistent with excessive cow milk intake and initial laboratory tests demonstrating hemoglobin concentration of 8.1 g/dL and MCV 58 fL. The second case was an otherwise well 15 year old girl with heavy menstrual bleeding (HMB) whose hemoglobin concentration was 9.5 g/dL and MCV 65 fL. Respondents were given the opportunity to enter free-text comments in response to many of the survey prompts.

Study Procedures

An invitation email including a survey link was sent to potential respondents and subsequently 2 and 6 weeks later to non-responders. Survey results were anonymous and collected through the REDCap system at UT Southwestern. (9) The survey instrument was reviewed by four local pediatric hematology/oncology physicians not involved with the study prior to its initiation to help ensure clarity and face validity. No assessment of test/re-test reliability was performed.

Analyses

Responses were included in the analysis if all questions related to the first case were addressed. Summary statistics included frequencies and cross-tabulations. In exploratory analyses, Pearson's χ^2 was used to evaluate associations between diagnostic and treatment recommendations and center and physician attributes. All analyses were completed with SAS 9.2 (SAS Institute, Cary, NC).

Results

A total of 1,217 physicians were surveyed, and 476 (39.1%) responded. Three hundred ninety-eight (83.6%) reported regularly treating IDA, completed the first case, and were therefore included in the analysis. Respondents represented a wide distribution of professional experience, center size, and geographic diversity (Table I). Most practiced both hematology and oncology (79%), and just over half the respondents reported having a fellowship program associated with their center (53%).

For Case 1, a toddler with nutritional IDA, the diagnostic approach was highly variable (Table II). While only 15% of respondents selecting the answer prompt "No testing beyond the CBC," most others indicated they would assess up to 8 additional laboratory studies among the options provided. The most frequently selected combination of iron-specific tests included serum ferritin, iron, and total iron binding capacity (TIBC) (N=93, 23%). In addition to the options listed, 5 respondents reported that stool guaiac testing would be part of their diagnostic evaluation.

The vast majority of respondents favored treatment with ferrous sulfate dosed at 6 mg/kg/day elemental iron in two divided doses. To determine if the degree of anemia influenced treatment decisions, respondents were asked the same dosing question for differing initial hemoglobin concentrations. Regarding iron therapy for patients with milder anemia (hemoglobin 10.1 g/dL rather than 8.1 g/dL), 35% indicated they would reduce the iron dose. While most (93%) would reduce to 3 mg/kg/day or 4 mg/kg/day, a few respondents (n=7 or 1.8%) reported recommending no treatment or a multivitamin with iron alone. For the most severe cases of IDA, respondents were asked about a hemoglobin value below which they would definitely transfuse. Approximately one third of respondents indicated there was no hemoglobin below which they would definitely transfuse, while the remaining respondents demonstrated remarkable variability from 3 g/dL up to 6 g/dL in a small minority. Free-text comments regarding transfusion threshold (n=8) reflected decision-making considerations such as family trust, distance from the hospital, other co-

morbid conditions, and prior success with oral iron therapy alone in patients with severe anemia.

For Case 2, the adolescent with IDA due to heavy menstrual bleeding (Table III), the most commonly selected treatment (87%) was ferrous sulfate dosed at 2–3 tablets daily rather than weight-based dosing. The most popular intravenous iron preparation recommended for those patients who failed oral iron therapy was iron sucrose (48%).

Exploratory analyses were performed to determine if time in practice, practice size and/or location, association with a fellowship program, and focus on hematology exclusively versus hematology and oncology were associated with specific IDA management decisions including diagnostic evaluation, iron preparation, dosing, and transfusion threshold. Increased time in practice, smaller practice size, and lack of an institutional fellowship program were associated with minimal diagnostic testing (no tests beyond the CBC) but no other features of clinical management (Table IV). No differences in practice patterns were noted between physicians who practice hematology exclusively versus those who practice both hematology and oncology. Similarly, no significant differences were observed between physician practice patterns based on geographic location.

Discussion

Despite IDA being the most common hematologic condition during childhood and adolescence, its optimal treatment approach is undefined, resulting in marked heterogeneity among recommended treatment strategies. Although IDA is often managed by primary care physicians, it is a common reason for consultation request from and/or referral to pediatric hematology/oncology specialists. Many such patients will already have failed oral iron therapy and thus are likely to present with more severe disease.

The variability in diagnostic approach to IDA deserves consideration. Many patients referred to a pediatric hematology/oncology specialist have had laboratory testing beyond a CBC, which may influence the types of testing subsequently performed. To minimize such influence, our survey prompt specifically stated that only a CBC had been performed prior to the initial visit. While many pediatric hematology/oncology experts recommend a “trial of iron” to be both diagnostic and therapeutic for what seems to be straight-forward IDA, only 15% of respondents indicated no additional testing being warranted in a classic case of nutritional IDA in a toddler. (10)

In patients found to be anemic on initial screening, guidelines from the American Academy of Pediatrics (AAP) Committee on Nutrition recommend that confirmatory testing for suspected IDA should include measurement of the reticulocyte hemoglobin content (CHr or Ret-He), serum transferrin receptor 1 (TfR1) concentration, and/or serum ferritin with C-reactive protein (CRP).(6) Of note, the AAP report does not mention that CHr cannot discriminate between thalassemia trait and IDA(11), nor that the TfR1 cannot discriminate between hemolytic anemia and IDA. Furthermore, such testing is not readily available in all institutions, thus limiting their utility in clinical decision making. Based on our survey results, the AAP’s approach to confirmatory testing is not employed by most pediatric

hematology/oncology physicians. Review of the CBC, reticulocyte count and peripheral smear along with serum iron, serum ferritin and total iron binding capacity is usually felt to provide firm evidence for or against a diagnosis of IDA,(12) with such tests being selected by over half of the survey respondents.

For treatment of IDA, respondents indicated that decision-making was based more on experience rather than evidence. Nearly all pediatric textbooks and review articles cite 3–6 mg/kg/day of elemental iron as effective IDA therapy, but few comparative studies of optimal iron preparations, doses, and/or schedules exist in the literature. (13–16) No data support iron dosing of 6 mg/kg/day in children, even though this was the overwhelming preference of physicians who responded to the survey. In contrast, several well-designed trials have demonstrated success with lower doses. A trial conducted in rural Ghana randomized patients to 40 mg of elemental iron, or approximately 3 mg/kg/day, either as a single dose or in three divided doses, with similar success in both arms. (17) A randomized trial in India compared ferrous ascorbate to colloidal iron as a single daily iron dose of 3 mg/kg/day. (18) Correction of the anemia occurred in both groups over a 12 week study period, supporting the efficacy of a once daily dose at the lower end of the recommended range. One study involving 90 elderly patients compared three daily dosing regimens of elemental iron (15 mg; 50 mg; 150 mg).(19) After two months, the increases in hemoglobin concentration and serum ferritin were similar in all three groups. Moreover, adverse effects and dropout rates were least frequent in the lowest dose group, highlighting that low dose oral iron therapy may be as effective as higher doses while also minimizing adverse effects that can contribute to poor adherence. Furthermore, in 1998 the CDC suggested a simplified regimen of 3 mg/kg/day of elemental iron given between meals for treatment dosing in young children to improve adherence. (20)

Regarding duration of continued therapy to reconstitute iron stores following resolution of anemia, survey respondents demonstrate a wide range of treatment practices. Research that better defines the expected resolution of hematologic and iron indices would allow for more clear definitions of IDA treatment success versus failure.

In adolescents, like in adults, iron dose recommendations are not supported by evidence. Considerations of the patient's weight, tolerability of high iron doses, and adherence are largely undetermined in this population. An appealing and more effective treatment option for such patients is intravenous iron, particularly when moderate to severe anemia has persisted despite physicians' and parents' best efforts to ensure compliance. (21) Despite the current availability of many effective intravenous iron preparations that have been FDA-approved for adults who do not respond to oral iron (due to suboptimal adherence, adverse effects, failure to correct the primary etiology, etc.) and their successful use in children,(22–24) 13% of survey respondents chose to continue oral iron therapy. Perhaps the safety concerns regarding intravenous iron preparations, such as the high molecular weight iron dextran employed in past years, have had a negative connotation affecting all intravenous iron preparations. Medication cost and ancillary charges for the infusion and patient monitoring may also play a role. However, several novel intravenous iron agents that can correct IDA with a single short infusion may prove beneficial in children who have failed oral iron therapy. (25)

Survey research clearly has many limitations. First, low completion rates may result in ascertainment bias. Response biases including social desirability bias may also have influenced the results, although such biases were minimized by the anonymous survey responses. Moreover, the validity of the survey instrument was not fully established with test/re-test reliability prior to administration. Nonetheless, to our knowledge no prior surveys regarding the treatment of IDA in children have been published with the aim of offering insights into the decision-making processes that affect their management.

In conclusion, the approach to diagnosis of IDA in childhood is widely variable among ASPHO members practicing in the United States. Treatment of IDA appears to be largely guided by personal experience rather than evidence, and marked variability is apparent in many aspects of IDA patient care. This practice continues because it is generally successful. However, given the prevalence of this condition both in the United States and globally, research that identifies the optimal management of IDA such as initial work-up, iron preparation, dosing and total duration of iron therapy, with consideration of cost-effectiveness, is of utmost importance. Randomized clinical trials of IDA treatment and formulation of evidence-based management guidelines for both toddlers and adolescents are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Respondent Demographics (n=398)

Demographic	Percentage of Respondents
Time in Practice	
0–5 years	26
6–10 years	19
11–15 years	10
>15 years	45
Practice Hematology exclusively or Hematology & Oncology	
Hematology only	21
Hematology & Oncology	79
Total number of physicians in practice	
1–2 physicians	8
3–5 physicians	27
6–10 physicians	30
>10 physicians	35
Local Fellowship Program	
No	46
Yes	53

Table II**Responses to Case 1: Toddler with Nutritional IDA**

Case Scenario (Abbreviated): A healthy 18-month-old male is referred for anemia. Diet consists of 32–40 oz whole cow milk daily and limited iron-rich foods. He is pale. His hemoglobin is 8.1 g/dL, RBC count 4 million/mm³, RDW 20%, and MCV 58 fL. No other laboratory tests were previously performed.

Scenario	Percentage
In addition to a CBC, which of the following tests would you routinely obtain when first seeing such a patient in your office? (select all that apply)	
No other tests necessary	15
Reticulocyte count	64
Serum ferritin	70
C-reactive protein (CRP)	1
Serum transferrin saturation	31
Serum iron	57
Hemoglobin electrophoresis	13
Serum transferrin receptor	3
Reticulocyte hemoglobin content (CHr or Ret-He)	6
Blood lead level	21
Total iron binding capacity	56
Other	6
Which oral iron preparation would you recommend (assuming insurance and access are not problematic)? (select one)	
Ferrous sulfate	84
Other iron salt	1
Iron polysaccharide	13
Carbonyl iron	2
Other	<1
Which factors contribute to your recommended oral iron preparation? (select all that apply)	
Previous successful experience with it	82
Medical literature (published clinical studies involving that iron formulation)	27
Cost / Insurance	59
Taste / Tolerability	30
Practice / Recommendation of your partner(s)	18
Recommendation of the hematologist(s) with whom you trained	29
Other	2
What total daily elemental iron dose would you recommend? (select one)	
3 mg/kg	11
4 mg/kg	23
6 mg/kg	62
Other	4

If the patient's hemoglobin was 6.1 g/dL (rather than 8.1), would you recommend a different total daily dose of elemental iron? (select one)

Case Scenario (Abbreviated): A healthy 18-month-old male is referred for anemia. Diet consists of 32–40 oz whole cow milk daily and limited iron-rich foods. He is pale. His hemoglobin is 8.1 g/dL, RBC count 4 million/mm³, RDW 20%, and MCV 58 fL. No other laboratory tests were previously performed.

Scenario	Percentage
No, I would give the same dose	84
Yes, I would recommend a different dose	16
Restricted to “yes” responses for recommending a different dose:	
What total daily dose would you recommend instead? (select one, N = 64)	
3 mg/kg	2
4 mg/kg	6
6 mg/kg	89
Other	3
If the patient’s hemoglobin was 10.1 g/dL (rather than 8.1), would you recommend a different total daily dose of elemental iron? (select one)	
No, I would give the same dose	65
Yes, I would recommend a different dose	35
Restricted to “yes” responses for recommending a different dose:	
What total daily dose would you recommend instead? (select one, N = 141)	
3 mg/kg	55
4 mg/kg	38
6 mg/kg	<1
Other	6
How would you divide the total daily iron dose? (select one)	
Once daily (QDay)	15
Divided into 2 doses (BID)	69
Divided into 3 doses (TID)	15
Other	2
What is the hemoglobin value below which you would definitely recommend a blood transfusion (assuming the child looks “well compensated” with no co-morbidities)? (select one)	
There is no hemoglobin below which I would definitely recommend a blood transfusion	35
3 g/dL	17
4 g/dL	23
5 g/dL	19
6 g/dL	3
Other	3
Case 1 Scenario (Continued): At a 12 week follow-up visit, the hemoglobin is 12.2 g/dL, MCV 78 fL and ferritin 25 ng/mL, and diet is improved.	
Would you recommend continued oral iron therapy? (select one, N = 397)	
No	33
Yes, 1–2 additional months of iron therapy	45
Yes, 3 or more additional months of iron therapy	20
Other	3

Table III**Responses to Case 2: Teenager with IDA due to HMB**

Case Scenario (Abbreviated): A healthy 15-year-old girl is referred for anemia. She has heavy menstrual periods but no evidence of a bleeding disorder, and is now on hormonal regulation. She has mild pallor. Her hemoglobin is 9.5 g/dL and MCV 65 fL and peripheral smear is consistent with iron deficiency.	
Scenario	Percentage
Which oral iron preparation would you recommend (assuming insurance and access are not problematic)? (select one, N = 394)	
Ferrous sulfate	83
Other iron salt	4
Iron polysaccharide	12
Carbonyl iron	<1
Other	<1
Would this patient's daily dose be based on number of tablets daily or on weight? (select one, N = 394)	
Number of tablets daily	64
Weight-based dosing	36
Restricted to "number of tablets daily" responses for dosing:	
What total daily elemental iron dose would you recommend? (select one, N = 253)	
1 iron tablet daily	8
2–3 iron tablets daily	87
Other	4
Restricted to "weight-based" responses for dosing:	
What total daily elemental iron dose would you recommend? (select one, N = 141)	
1–2 mg/kg	11
3–4 mg/kg	82
Other	8
How would you divide the total daily iron dose? (select one, N = 394)	
Once daily (QDay)	16
Divided into 2 doses (BID)	71
Divided into 3 doses (TID)	11
Other	1
Case 2 Scenario (Continued): At 4 week visit, she reports stopping oral iron medication due to GI side effects. Laboratory studies are unchanged. You change to another oral iron preparation, but she reports poor compliance. You describe parenteral iron treatment options, and she is interested.	
Which intravenous iron preparation would you recommend? (select one, N = 392)	
Iron sucrose	48
Low molecular weight iron dextran	15
High molecular weight iron dextran	3
Ferumoxytol	1
Ferric gluconate	17
Continue oral iron therapy	13
Other	2

Table IV

Exploratory Analysis of Demographic Factors and Diagnostic testing

Additional Lab Studies Other Than CBC		No Additional Lab Studies Other Than CBC		P
Time in Practice				
5 years	89.3	10.7		0.005
6 – 10 years	90.5	9.5		
> 15 years	78.2	21.8		
Number of Physicians				
1–5	78.4	21.6		0.035
6–10	86.8	13.2		
> 10	89.1	10.9		
Fellowship Program				
No	80.7	19.3		0.037
Yes	88.2	11.8		