# Trends in Anemia, Iron, Therapy, and Transfusion in Hospitalized Pediatric Patients with Inflammatory Bowel Disease

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**Objective** To evaluate trends in diagnosis and management of iron deficiency anemia using a large national children's hospital database in pediatric patients admitted with inflammatory bowel disease (IBD).

**Study design** In this retrospective multicenter cohort study, we used the Pediatric Health Information System de-identified administrative database. Patients age <21 years with ≥2 admissions with *International Classification of Disease, Ninth Revision and Tenth Revision* codes for Crohn's disease or ulcerative colitis from 2012 to 2018 were included. We extracted data regarding diagnoses of anemia and/or iron deficiency, and receipt of oral iron, intravenous (IV) iron, and/or blood transfusion. Data were analyzed descriptively.

**Results** We identified 8007 unique patients meeting study criteria for a total of 28 260 admissions. The median age at admission was 15.4 years. A diagnosis of anemia was documented in 29.8% of admissions and iron studies were performed in 12.6%. IV iron was given in 6.3% of admissions and blood transfusions in 7.4%. The prevalence of the diagnosis of anemia among IBD admissions increased from 24.6% in 2012 to 32.4% in 2018 ($P < .0001$). There was a steady increase in the proportion of IBD admissions that used IV iron, from 3.5% in 2012 to 10.4% in 2018 ($P < .0001$), and the proportion of admissions with red cell transfusions decreased over time from 9.4% to 4.4% ($P < .0001$).

**Conclusions** Iron deficiency anemia is prevalent among pediatric patients with IBD admitted to US children's hospitals. From 2012 to 2018, there was an increase in the use of inpatient IV iron for the treatment of iron deficiency anemia and a decrease in transfusions. *(J Pediatr 2020;222:141-5)*.

Anemia is the most common extraintestinal symptom in children with inflammatory bowel disease (IBD) and is present in up to three-quarters of patients, most commonly owing to iron deficiency.[1,2] Even during states of remission, ≤85% of children with IBD are iron deficient, with up to one-third of these having progressed to iron deficiency anemia (IDA).[3] Iron deficiency, even without anemia, has significant impact on health-related quality of life and has been associated with cognitive dysfunction, impaired physical performance, decreased exercise tolerance, dizziness, fatigue, headache, shortness of breath, and restless legs syndrome.[4,5] Iron deficiency can also exacerbate the risk of venous thromboembolism in patients with IBD.[6]

Despite its prevalence and impact, iron deficiency remains underrecognized and undertreated in children with IBD.[7,8] Oral iron supplementation is often considered ineffective for such patients owing to gastrointestinal intolerance, suboptimal absorption, and the potential to worsen local disease inflammation within the gastrointestinal tract.[3] In adults with IBD, intravenous (IV) iron is commonly used and capable of normalizing iron status, even in the setting of persistent inflammation.[9-11] Newer IV iron formulations with decreased dosing requirements and improved safety profiles have reduced barriers to its use in pediatric patients.[12] However, minimal published data exist on the use of IV iron in pediatric IBD.

Although allogeneic red blood cell transfusions were commonly used to treat anemia in IBD in the past, the current European Crohn and Colitis Organization's consensus guidelines recommend blood cell transfusion only for severe symptomatic anemia with hemodynamic instability, life-threatening anemia, or in the case of severe acute gastrointestinal hemorrhage.[9] Red blood cell transfusions are not without significant risks including hemolytic transfusion reactions, febrile nonhemolytic transfusion reactions, transfusion-related acute lung injury, and potential for transmission of infectious diseases.[13]

Our objective was to evaluate trends in the diagnosis of IDA and its management in pediatric patients with IBD using a large national children's hospital database over a 7-year period. We hypothesized that the use of IV iron to treat

| | |
|---|---|
| IBD | Inflammatory bowel disease |
| IDA | Iron deficiency anemia |
| IV | Intravenous |
| PHIS | Pediatric Health Information System |

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IDA would increase and receipt of blood transfusion would subsequently decrease over time.

## Methods

In this retrospective multicenter cohort study we used the Pediatric Health Information System (PHIS) de-identified administrative database. The PHIS database contains comprehensive inpatient data from 48 not-for-profit tertiary care pediatric hospitals, representing about one-quarter of pediatric centers in the US. Participating institutions represent diverse geographic locations, bed number, and average daily census, and are affiliated with the Children's Hospital Association (Overland Park, Kansas). Each patient has a unique identification number, allowing them to be followed over time. The data warehouse is managed by Truven Health Analytics (Ann Arbor, Michigan), and assurance of data quality and reliability is a joint effort between the Children's Hospital Association and participating hospitals. Because all data in the PHIS dataset are de-identified, this study did not qualify as human subject research and was considered exempt by the Nationwide Children's Hospital Institutional Review Board.

Patients were all children and young adults age <21 years admitted for IBD to a PHIS hospital between January 1, 2012, and December 31, 2018. *International Classification of Disease, Ninth Revision and Tenth Revision*, codes were used to identify all inpatient admissions with an IBD diagnosis during this time frame. To exclude patients who may have been admitted once to evaluate for IBD but did not subsequently have a confirmed diagnosis, we only included patients with an IBD code documented in ≥2 separate admissions during the study period. Diagnostic codes were also used to identify those patients with anemia or iron deficiency during their admission (**Table I**; available at www.jpeds.com). Evaluation for iron deficiency was defined as an assessment of serum ferritin, transferrin, total iron-binding capacity, and/or serum iron during the hospitalization. Procedure codes were assessed for receipt of blood transfusions and pharmaceutical billing codes were used to determine if iron therapy (either oral and/or IV preparations) were given during admission (**Table I**). Additionally, billing codes for physician subspecialty (hematology or gastroenterology) were used to determine if patients were admitted to or received a consult from one of these services. Demographic data including race, ethnicity, insurance type, and geographic region were also extracted from the PHIS database. We did not have access to numeric laboratory values using the PHIS database.

All data were summarized using descriptive statistics, frequency, and percentage for categorical variables and median and range for continuous variables. We used $\chi^2$ tests to compare proportions between groups and to assess the change in proportions over time. Comparisons of continuous values between groups, such as length of stay, were performed using Mann-Whitney *U* tests. *P* values of <.05 were considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

## Results

We identified 8007 unique patients with ≥2 admissions with IBD diagnosis codes from 2012 through 2018 for a total of 28 260 admissions. The median patient age at admission was 15.4 years (range, 0-21.9 years). The majority of patients (57.6%) had private insurance. Additional demographic data are listed in **Table II**. A diagnosis of anemia was documented in 8412 admissions (29.8%; 95% CI, 29.2%-30.3%) and in 2040 unique patients (25.5%; 95% CI, 24.5%-26.5%). A complete blood count was obtained during 24 629 (87.2%) admissions and in 6549 patients (81.8%). There was no clinically meaningful change in the percentage of patients who had complete blood counts over the 7-year study period (data not shown). Hemoglobin and/or hematocrit were obtained in 4007 admissions (14.2%) and in 967 patients (12.1%). Laboratory assessment for iron status was performed in 3562 admissions (12.6%). The most common assessment among these was serum iron, performed in 2984 admissions (10.6%; **Table III**).

Any form of iron therapy (oral or IV) was administered in 6493 admissions (23%), IV iron was given in 6.3% of admissions, and red cell transfusions were given in 7.4% of admissions (**Table III**). Over the study period, a diagnosis of anemia among IBD admissions increased from 24.6% in 2012 to 32.4% in 2018 ($P < .0001$). Laboratory assessment

**Table II. Demographics of admissions for pediatric patients with IBD in US children's hospitals**

| Characteristics | Number (%) or median (range) |
|---|---|
| Total admits | 28 260 |
| Total unique patients | 8007 |
| Age at admission | 15.4 (infant – 21.9) |
| Male sex | 14 121 (50.0) |
| Race | |
| White | 19 536 (69.1) |
| Black | 4304 (15.2) |
| Asian | 527 (1.9) |
| Native American/Pacific Islander | 155 (0.5) |
| Other/unknown | 3738 (13.2) |
| Ethnicity | |
| Non-Hispanic/Latino | 23 280 (82.4) |
| Latino/Hispanic | 3405 (12.1) |
| Unknown | 1575 (5.6) |
| Insurance type | |
| Public (CHIP, Medicaid) | 10 638 (37.6) |
| Private | 16 265 (57.6) |
| Other (charity, self-pay) | 1062 (3.8) |
| Unknown | 295 (1.0) |
| Geographic region | |
| Midwest | 7740 (27.4) |
| Northeast | 6007 (21.3) |
| South | 8981 (31.8) |
| West | 5532 (19.6) |

*CHIP*, Children's Health Insurance Program.

**Table III. Assessment and management of IDA in admissions of pediatric patients with IBD (PHIS data source, 2012-2018)**

| Variables | Admissions, n (%) | Patients, n (%) |
|---|---|---|
| Laboratory evaluations | | |
| Any iron laboratory assessment | 3562 (12.6) | 816 (10.2) |
| Ferritin | 2675 (9.5) | 633 (7.9) |
| Transferrin | 862 (3.1) | 206 (2.6) |
| Total iron-binding capacity | 2413 (8.5) | 528 (6.6) |
| Serum iron | 2984 (10.6) | 660 (8.2) |
| Inpatient iron management | | |
| Packed red blood cell transfusion | 2078 (7.4) | 460 (5.7) |
| Iron therapy | 6493 (23.0) | 1587 (19.8) |
| Oral iron | 5201 (18.4) | 1258 (15.7) |
| IV iron | 1777 (6.3) | 448 (5.6) |

for iron status increased over time from 10.2% to 15.4% ($P < .0001$). There was an increase in the proportion of IBD admissions that used IV iron, from 3.5% in 2012 to 10.4% in 2018 ($P < .0001$). The proportion of admissions for IBD with red cell transfusions decreased over time from 9.4% to 4.4% ($P < .0001$; Figure). In the 2078 admissions, which included a red cell transfusion, IV iron was coadministered in 268 of these admissions (12.9% of transfusion admissions), and any type of iron (oral or IV) was coadministered in 868 of these admissions (41.8%).

Patients with a longer length of stay were more likely to receive IV iron (7 days vs 4 days; $P < .0001$). Of all US regions, the Northeast region used IV iron more frequently than others (8.6% of admissions), but not by a clinically large margin (West 6.6%, Midwest 6.2%, South 4.6%, $P < .0001$). We did not find any clinically meaningful differences in use of IV iron by race or ethnicity. Patients who had a hematology consult during their admission were much more likely to receive IV iron (18.3%) compared with those without a hematology consult (6.1%) ($P < .0001$; OR, 3.5).

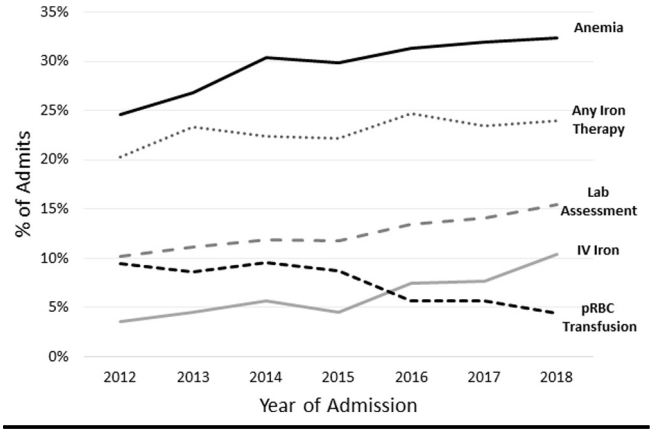


**Figure.** Trends in anemia diagnosis and therapies in admissions of pediatric patients with IBD (PHIS data source, 2012-2018). *pRBC*, packed red blood cells.

Admissions involving a hematology consult were, like IV iron, more likely to have a packed red blood cell transfusion (20%) compared with admissions without hematology involvement (7.2%) ($P < .0001$). Of all IV iron formulations, the most commonly used was iron sucrose (4.4% of total admissions). Ferric gluconate and iron dextran were used less frequently (0.9% and 0.8% of total admissions, respectively). The remaining admissions that included IV iron used ferric carboxymaltose or ferumoxytol.

## Discussion

This study was designed to assess trends in anemia diagnosis and use of IV iron and blood transfusions in pediatric patients with IBD over a 7-year period in a national children's hospital database. Our study demonstrates that documentation of an anemia diagnosis has significantly increased over time, suggesting improved recognition of this complication. Iron deficiency is the most common cause of anemia in IBD; however, in our study, assessment of iron status was performed in <15% of admissions. We identified a significant decrease in admitted patients receiving transfusions and an increase in the use of IV iron for the treatment of IDA over time, yet overall treatment remains low.

IDA in patients with chronic diseases is commonly overlooked. Between 13% and 90% of adult patients with IBD have iron deficiency, with or without anemia, yet more than one-half of those diagnosed with IDA are not treated.[14] At least 1 study comparing pediatric and adult patients with IBD found that 70% of children had anemia, compared with 40% of adults; 88% of children were iron deficient compared with 55% of adults.[7] In another large cohort study of outpatient encounters in children with IBD, >80% were screened for anemia but only 24% of anemic patients were tested specifically for iron deficiency.[8] In our study, despite an upward trend in anemia diagnoses among pediatric admissions with IBD, overall the prevalence was <35%, which is much lower than previous reports. Our lower prevalence could be due to our data source, which depends on formal documentation and appropriate coding of IDA by providers, but it could also be due to ongoing under-recognition.

In regard to treatment of anemia in pediatric IBD, a single-institution study found that only 13% of iron-deficient children with IBD were given iron supplementation and none were given IV iron in comparison with 30% of adolescents and 41% of adults.[7] Similarly, an analysis of a US commercial claims database revealed that <10% of children with IDA were treated with IV iron.[8] Large published trials in adult patients with IBD have shown that IV iron is a safe, effective, and well-tolerated intervention for correcting IDA and maintaining iron stores.[15-21] According to European Crohn and Colitis Organization consensus guidelines, IV iron should be considered first line therapy for iron deficiency in patients with IBD with clinically active disease, hemoglobin <10 g/dL (equivalent to >2 g/dL below the lower limit of normal for age in the pediatric population), or previous intolerance to oral iron.[9] Despite the European Crohn and Colitis Organization's

recommendations and an abundance of evidence in adult patients with IBD, our study suggests that the use of IV iron for correction of IDA in pediatric patients with IBD remains low.

Blood transfusion to correct anemia in IBD is only indicated to treat severely symptomatic or life-threatening anemia, or acute severe hemorrhage.[9] Although we found that the number of patients receiving blood transfusions was similar to the number receiving IV iron, we were encouraged with the significant upward trend in IV iron administration and downward trend in blood transfusions during our study timeframe (2012-2018). We postulate that as IV iron becomes a more widely accepted treatment for anemia in IBD, the number of patients receiving blood transfusions will continue to decrease. Even if a blood transfusion is given to correct symptomatic anemia, iron supplementation in addition to transfusion is still required because the iron in transfused blood will not be available for further hematopoiesis until the transfused blood cells are broken down and their iron is recycled, a process that could take up to 3 months. In our study cohort, fewer than one-half of patients receiving a blood transfusion also received iron supplementation.

Although the PHIS database is comprehensive and representative of inpatient practice in US tertiary care children's hospitals, there are several limitations, including those germane to any database (missing data, coding errors, and sampling errors). The overall use of IV iron in patients with IBD is underestimated in this database because we did not have access to IV iron given in outpatient settings. Given that we only had inpatient data, the number of patients in whom iron studies were obtained may be underestimated because outpatient data were not captured. However, in a recent study looking at screening for iron deficiency with iron studies in an outpatient population of children and adolescents with IBD, a similar low screening rate was found (<25%).[8] Additionally, we do not have access to specific components of medical records or medical decision making and thus were unable to determine clinical indications for blood transfusions from an administrative database. It is possible that many transfusions were indicated per current consensus guidelines. Finally, because our study required >2 admissions with an IBD diagnosis code per patient, our included population is skewed toward patients with more severe disease.

In conclusion, our study demonstrated that anemia is prevalent among pediatric patients with IBD admitted to US children's hospitals. The increasing frequency of IDA during this 7-year study period may potentially be due to increased recognition of this complication. Regarding management, we identified an increase in the use of IV iron for the treatment of IDA over time, and a decrease in admitted patients receiving transfusions. Further research is needed to further optimize detection of iron deficiency in pediatric patients with IBD and establish the safety and efficacy of IV iron in this patient population. ■

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## Data Statement

Data sharing statement available at www.jpeds.com.

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## 50 Years Ago in *The Journal of Pediatrics*

### Predictors of Severity of Iron Poisoning

James JA. Acute Iron Poisoning: Assessment of Severity and Prognosis. J Pediatr 1970;77:117-9.

Fifty years ago, James categorized 59 children with acute iron poisoning into mild (n = 18), moderate (n = 12), and severely affected (n = 29) based on their symptoms. He also described a ferrous sulphate dose of >20 tablets (equivalent to 6 grams of iron), and a serum iron concentration >500 $\mu$g/mL within 4 hours of admission as significant measures to determine severe toxicity. A total of 38 children received deferoxamine and improved. There were no deaths. The author concluded that assessment of severity based on examination alone can be misleading, and that other measures, including laboratory tests and radiography, should be included for predicting disease severity.

Iron tablets can be unintentionally ingested by children because they are brightly colored and sugar-coated. Children who ingest <20 mg/kg of elemental iron are mostly asymptomatic; however, ingestion of 20-40 mg/kg produces moderate symptoms, and >60 mg/kg results in severe toxicity.[1] A lethal dose of iron is 200-250 mg/kg. Iron poisoning initially manifests as vomiting and diarrhea due to gastric irritation within 6-8 hours of ingestion, followed by a latent phase up to 24 hours when iron is absorbed from the gastrointestinal tract and distributed to other organs. The symptoms may completely subside after the latent period, or the patient may deteriorate further with metabolic acidosis, shock, and acute liver failure. Gastric stricture is a late complication that occurs between 2-4 weeks. It is important to determine the severity early in the course of disease to intervene at the appropriate time and prevent morbidity and mortality.

Serum iron concentration helps confirm iron toxicity if samples are obtained at the appropriate time: 4-6 hours after ingestion of regular iron and 8 hours for extended-release iron preparations. A combination of clinical and laboratory measures can help determine the severity of poisoning. Ingestion of >60 mg/kg of iron, presence of symptoms, serum iron concentration >500 $\mu$g/mL, hyperglycemia (>150 mg/dL), leukocytosis (>15 000/mm$^3$), and presence of iron tablets on abdominal radiograph indicate severe toxicity and hence the need to administer intravenous desferroxamine therapy.[2] Our understanding of factors determining severity of iron poisoning has undergone little change over the past half-century.

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**Table I. Diagnostic and procedure codes used for PHIS search**

| PHIS search strategies | Codes and information |
|---|---|
| Inclusion criteria | Inpatient admits from 2012 through 2018 |
| Age at admit | <21 years |
| DX of IBD | Require patients to be admitted with an IBD code twice during the study period |
| Crohn's disease | ICD-9: 555.x |
| | ICD-10: K50x |
| Ulcerative colitis | ICD-9: 556.x |
| | ICD-10: K51x |
| Other diagnoses of interest | |
| Anemia | ICD-9: 280.x, 285.1, 285.9 |
| | ICD-10: D50x, D62, D649, D6489 |
| Medications of interest | |
| IV iron | 144035 – Iron Sucrose |
| | 144031 – Sodium Ferric Gluconate Complex |
| | 144025 – Iron Dextran |
| | 144027 – Ferumoxytol |
| | 144003 – Ferric Carboxymaltose |
| Oral iron | 144001 – Ferrous Sulfate (exsiccated) |
| | 144021 – Iron Polysaccharide complex |
| | 144015 – Carbonyl Iron |
| | 144011 – Ferrous Gluconate |
| | 144005 – Ferrous Fumarate |
| Steroids | 154035 – Dexamethasone |
| | 154071 – Methylprednisolone |
| | 154081 – Prednisolone |
| | 154083 – Prednisone |
| Procedures of interest | |
| Blood transfusion | ICD-9: 99.03, 99.04, 99.06, 99.07, 99.09 |
| | ICD-10: 30230N1, 30233H1, 30233N1, 30233P1, 30240N1, 0243N1, 30243P1, 30263N1, 30277N1 |
| Colonoscopy | ICD-9: 45.23 |
| | ICD-10: 0DFD8ZZ |
| Laboratory tests of interest | |
| Ferritin | 318311 |
| Transferrin/sTfR | 318331 |
| TIBC | 311241 |
| Serum iron | 311240 |
| Complete blood count | 322200 (unspecified) |
| | 322210 (with differential) |
| | 322220 (without differential) |
| Hemoglobin | 324002 |
| Hematocrit | 321110 |
| Hemoglobin and hematocrit | 322240 |

*ICD9/10*, International Classification of Disease, Ninth Revision and Tenth Revision; *sTfR*, soluble transferrin receptor; *TIBC*, total iron-binding capacity; *DX*, Diagnosis.