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Original Article

Anemia Screening, Prevalence, and Treatment in Pediatric Inflammatory Bowel Disease in the United States, 2010–2014

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Conflict of Interest
The remaining authors (Carmelo Cuffari, Eboselume Akhuemonkhan, Anthony L. Guerrerio, Harold Lehmann) have no relevant sources of funding or conflicts of interest to declare.

ABSTRACT

Purpose: We examined the prevalence of anemia, annual screening for anemia, and treatment of anemia with iron among children with inflammatory bowel disease (IBD).
Methods: A retrospective study of U.S. pediatric patients with IBD was performed in the MarketScan commercial claims database from 2010–2014. Children (ages 1–21) with at least two inpatient or outpatient encounters for IBD who had available lab and pharmacy data were included in the cohort. Anemia was defined using World Health Organization criteria. We used logistic regression to determine differences in screening, incident anemia, and treatment based on age at first IBD encounter and sex.
Results: The cohort (n=2,446) included 1,560 Crohn's disease (CD) and 886 ulcerative colitis (UC). Approximately, 85% of CD and 81% of UC were screened for anemia. Among those screened, 51% with CD and 43% with UC had anemia. Only 24% of anemia patients with CD and 20% with UC were tested for iron deficiency; 85% were iron deficient. Intravenous (IV) iron was used to treat 4% of CD and 4% UC patients overall and 8% of those with anemia.
Conclusion: At least 80% of children with IBD were screened for anemia, although most did not receive follow-up tests for iron deficiency. The 43%–50% prevalence of anemia was consistent with prior studies. Under-treatment with IV iron points to a potential target for quality improvement.

Keywords: Crohn disease; Screening; Ulcerative colitis; Anemia; Iron-deficiency

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the chronic inflammatory bowel disease (IBD) [1]. Up to 25% of patients with IBD are diagnosed in childhood or adolescence, and the incidence is increasing [1,2]. In addition to the typical symptoms of IBD such as bloody

stools and abdominal pain, IBD is associated with a multitude of systemic complications, the most prevalent of which is anemia [3].

Anemia significantly worsens quality of life in patients with IBD [4,5], and anemia can result in worsened cognitive outcomes [6]. The most common etiologies of anemia in children with IBD are iron deficiency and anemia of chronic disease [7]. Iron deficiency anemia can result from insufficient dietary iron intake due to altered diet, diminished uptake in the small bowel, and chronic blood loss due to mucosal ulcerations [8]. Both iron deficiency anemia and anemia of chronic disease are associated with ongoing inflammation [3,4,8,9]. Other risk factors associated with development of anemia among children with IBD include more extensive disease [2,5,8-10], poor growth [4,9], presence of CD as opposed to UC [8], and African American ethnic background [7]. Diagnosis of anemia in pediatric IBD is made according to World Health Organization (WHO) standards for hemoglobin (Hgb) and hematocrit (Hct) by age (**Supplementary Table 1**) [7,11]. When anemia is present, iron deficiency and anemia of chronic disease are diagnosed with further laboratory tests, including ferritin and C-reactive protein (CRP) [7].

The pathways from screening to diagnosis and then treatment of anemia among children with IBD are based on guidelines for adults with IBD published in 2007 [9] and 2015 by the European Crohn's and Colitis Organization (ECCO) [7]. Pediatric IBD guidelines suggest screening for anemia and iron deficiency during outpatient visits [12], but these recommendations lack specificity, so in practice the adult guideline is used. ECCO recommends at least annual measurement of Hgb/Hct for anemia, screening for iron deficiency after anemia is diagnosed, and treatment with intravenous (IV) iron among patients with active disease and oral iron for those with controlled disease who can tolerate the gastrointestinal side effects. Recent studies have suggested that oral iron use may trigger mucosal harm or adverse events not triggered by IV iron [10,13,14] and that IV iron results in rapid and complete resolution of anemia in children [15-17]. Choice of route therefore depends on disease activity, degree of anemia and oral iron tolerance [7].

Previous small to medium sized studies conducted in referral centers found that anemia is common in pediatric patients with IBD and these patients often go untreated, similar to adult IBD [3,4,18-37] (**Table 1**). No studies have examined adherence to anemia screening guidelines in pediatrics.

We examined the prevalence, screening and treatment of anemia as well as associated factors in a real-world cohort of pediatric IBD patients using MarketScan® Claims and Encounters database 2010–2014.

MATERIALS AND METHODS

This is a retrospective study of children with IBD using the MarketScan database from 2010–2014. This database contains information obtained from large employers, health plans, government, and public organizations. MarketScan incorporates billing data, labs, and pharmacy data from both inpatient and outpatient contexts for patients with private insurance including all 50 states [38]. The database consists of encounters of insured employees and their dependents through employer provided health insurance plans. Patients who received Medicaid or Medicare were not included. Claims from individuals who switch health plans during their employment are included. However, claims are not linked across employers.

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Table 1. Summary of the 17 studies on prevalence and treatment of anemia among children with IBD

Author; Location	Year	No. of pediatric IBD patients	Prevalence of anemia among screened patients	Prevalence of Fe treatment
Miller; United States*	2018	CD n=1,560* UC n=886*	CD 49%* UC 43%*	CD IV Fe 4%* UC IV Fe 3%*
Wikholm; Sweden	2016	CD n=28 UC n=45 IBDU n=17	46%†	Oral Fe 40%† Oral + IV Fe 4%† IV Fe 3%†
Sjöberg; Sweden	2014	CD n=44 UC n=38	55%†	Not reported
Van Biervliet; Belgium	2014	CD n=83	CD 61%	CD Oral Fe 12% CD IV Fe 4%
Gerasimidis; United Kingdom	2013	CD n=122 UC n=51 IBDU n=11	CD 72% UC 69% IBDU 66%	CD Oral Fe 34% UC Oral Fe 58%
Goodhand; United Kingdom	2012	CD n=73 UC n=31 IBDU n=9	57%†	Oral Fe 20%† IV Fe 10%†
Wiskin; United Kingdom	2012	CD n=46 UC n=34	75%†	Not reported
White; United States	2008	CD n=860 UC n=409 IBDU n=137	20%†	Not reported
Mack; United States and Canada	2007	CD n=392 UC n=134	CD 69% UC 36%	Not reported
Howarth; United Kingdom	2007	n=32†	63%†	Not reported
Thayu; United States	2005	CD n=78	CD 77%	Not reported
Khan; United States	2002	UC n=51 CD n=39	CD 41% UC 41%	Not reported
Revel-Vilk; Israel	2000	CD n=50 UC n=13	41%†	Not reported
Gryboski; United States	1994	CD n=40 UC n=38	CD 75% UC 84%	Not reported
Thomas; United States	1989	CD n=24	CD 71%	Not reported
Burbige; United States	1979	CD n=58	CD 50%	Not reported
Beeken; United States	1975	CD n=11	CD 73%	Not reported

Review of the published literature on incidence and rates of treatment of anemia in pediatric IBD.
IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, IBDU: inflammatory bowel disease unspecified, IV: intravenous, Fe: iron, n: the number of pediatric patients in the study.
*Current study; †IBD subtype not specified, aggregate counts only provided.

Children and young adults with at least two inpatient or outpatient encounters for IBD based on International Classification of Diseases, Ninth Edition, Clinical Modification codes 555 for CD or 556 for UC were eligible. Patients age 1 to 21 years old were included. Patients less than 1 year old were excluded as data suggests they have a greater likelihood of monogenic IBD, which is a distinct pathophysiologic entity [39]. Other exclusion criteria included lack of lab or pharmacy benefit. Patients with more encounters for CD than UC were classified as CD and similarly for UC. Patients with UC were censored at the time of colectomy. Lab tests were identified using Logical Observation Identifiers Names and Codes (LOINC) [40].

Anemia was defined using WHO standards for age (**Supplementary Table 1**). Individuals with anemia were assessed for iron-deficiency per WHO standards using ferritin <30 ng/mL for individuals with normal CRP and ferritin <100 ng/mL for individuals with elevated CRP [7]. Adherence to annual screening was examined by calculating yearly intervals from the patient's first date of anemia screening allowing a 3-month annual leeway period. Dates of inpatient stay were used as proxy dates for anemia screening because inpatient laboratory claims are not available. Laboratory values were required for contribution to the anemia

prevalence analysis. This methodology was outlined in a prior paper [35]. Anemia treatment was determined by prescriptions for oral or IV iron medications or by Current Procedural Terminology codes for infusion. Other demographic and clinical factors were assessed for each patient including sex, age, number of IBD outpatient visits, number of hospital admissions, and medications used for treatment of IBD.

Statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Frequency distributions, median and range for demographic values were calculated. Prevalence of screening for anemia was calculated based on the number of individuals who had a test result for Hgb, Hct or an inpatient stay after their first IBD encounter over the total eligible population. Inpatient stay was used as a proxy for screening given the common clinical practice of obtaining Hgb/Hct on children admitted to the hospital who have IBD. Frequency of testing was calculated to assess annual screening recommendation by examining the proportion of IBD patients with at least one screening or inpatient stay per year after their first test. Prevalence of anemia was calculated by dividing the number of individuals who met WHO criteria for anemia over the study period by the total number of individuals with Hgb or Hct results. Iron deficiency was assessed using the WHO standards. Prevalence of iron treatment was calculated by dividing the number of individuals who received oral or IV iron during the study period by the total number of IBD patients and separately among those with anemia. Logistic regression was used to examine age and sex differences in screening, prevalence of anemia and treatment. The Johns Hopkins Institutional Review Board approved this study (IRB00054790).

RESULTS

Demographics

Of 380,386 patients with at least two IBD encounters during 2010–2014, 44,862 had pharmacy benefit and laboratory information available and 2,446 (1,560 CD and 886 UC) were aged 1–21 with sufficient follow-up (**Supplementary Fig. 1**). Included individuals were predominately adolescents (median age 17 years for CD and 18 years for UC), almost equally split between male and female (48% female CD, 53% female UC), and had a median follow-up of 2 years for both CD and UC. The 35% of CD and 27% of UC patients had at least one IBD-related hospitalization. The 67% of CD and 50% UC had ten or more IBD-related outpatient visits. Steroids were the most common medication used by CD patients (55%) and aminosalicylates were the most common medication in UC (65%) (**Table 2**).

Prevalence of anemia screening

Among patients with CD, 85% were screened for anemia at least once, while 81% of UC patients were screened (**Fig. 1**). For patients with CD, there was no significant difference between males and females (chi-squared p=0.99), though for UC, males were screened more (chi-squared p=0.02) (**Table 3**). For patients with CD, children aged 12–13 were screened more than other age categories (chi-squared p=0.05). Patients with UC had no differences by age (**Table 3**).

Prevalence of anemia among those screened

Among screened patients (n=1,849), anemia was present in 51% of CD and 43% of UC patients (**Fig. 1**). For both CD and UC patients, females were more often anemic than males (chi-squared p<0.01). Patients with CD had no differences by age, but children with UC aged

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Table 2. Demographic characteristics of children with IBD

Characteristics	CD (n=1,560)	UC (n=886)
Median age at enrollment (Min–Max)	17 y (1–21)	18 y (1–21)
1–4	1.1	1.8
5–11	14	12.5
12–13	9.9	7.6
14–21	75	78.1
Female	48.4	53.4
Median length of follow-up after first IBD encounter (Min–Max)	2 y (1–4.9)	2 y (1–4.9)
IBD Hospitalizations		
0	65.1	73.4
1	19.3	18.2
2	7.2	4.2
≥3	8.4	4.3
Outpatient IBD visits		
1–10	33.3	50.1
10–20	26.2	25.3
20–50	33	21.2
≥50	7.5	3.4
Ever use of IBD-related medications		
Biologic	40.1	8.6
Immunomodulator	43.5	32.3
Steroid	55.2	57.6
5-ASA	26.6	65

Demographic characteristics of the cohort including age, sex, follow-up, hospitalizations and outpatient visits for IBD and IBD medications. Age, gender, and hospitalizations are presented as % of overall cohort. IBD medications are presented as % of the cohort who has used each medication.
IBD: inflammatory bowel disease, 5-ASA: mesalamine-containing medication.

12–13 were more often anemic than other groups (chi-squared p=0.03) (**Table 3**). Of the CD patients with CRP results (n=739), 60% of anemic patients had elevated CRP while 27% of non-anemic patients had elevated CRP. Of the UC patients with CRP results (n=343), 45% of anemic patients had elevated CRP while 19% of non-anemic patients had elevated CRP.

Prevalence of iron deficiency among those with anemia

Among patients who met WHO criteria for anemia (n=869), 24% of CD patients and 20% of UC patients had an associated ferritin and CRP measurement and could be assessed for iron-

Table 3. Anemia Screening, Prevalence, and Treatment by Age and Sex Among Children with IBD

Characteristics	Age (y)	CD (%)		Age p-value	UC (%)		Age p-value
		Male	Female		Male	Female	
Screening	1–4	87.5	77.8	0.71	91.0	100.0	0.25
	5–11	87.8	86.5	0.52	82.2	84.9	0.39
	12–13	75.9	83.8	0.05	84.4	70.0	0.48
	14–21	85.9	85.2	Reference	84.4	77.4	Reference
	Sex p-value	0.99			0.02		
Anemia prevalence	1–4	50.0	50.0	0.98	14.3	0.0	0.09
	5–11	43.8	45.5	0.31	33.3	46.0	0.59
	12–13	50.9	57.4	0.32	42.9	80.0	0.03
	14–21	42.4	56.3	Reference	37.3	48.3	Reference
	Sex p-value	<0.01			<0.01		
Treatment	1–4	0.0	0.0	0.98	0.0	0.0	0.99
	5–11	2.4	6.3	0.36	2.2	1.5	0.13
	12–13	3.5	1.5	0.12	2.7	0.0	0.22
	14–21	4.3	7.4	Reference	4.1	6.2	Reference
	Sex p-value	0.02			0.32		

Results are presented here of % patients screened for anemia, % patients with anemia, and % patients treated for anemia broken down by IBD subtype, age, and sex. The p-values were generated from logistic regression models; age is adjusted for sex and vice versa. The p-values are provided to 2 decimal places.
CD: Crohn's disease, UC: ulcerative colitis, IBD: inflammatory bowel disease.

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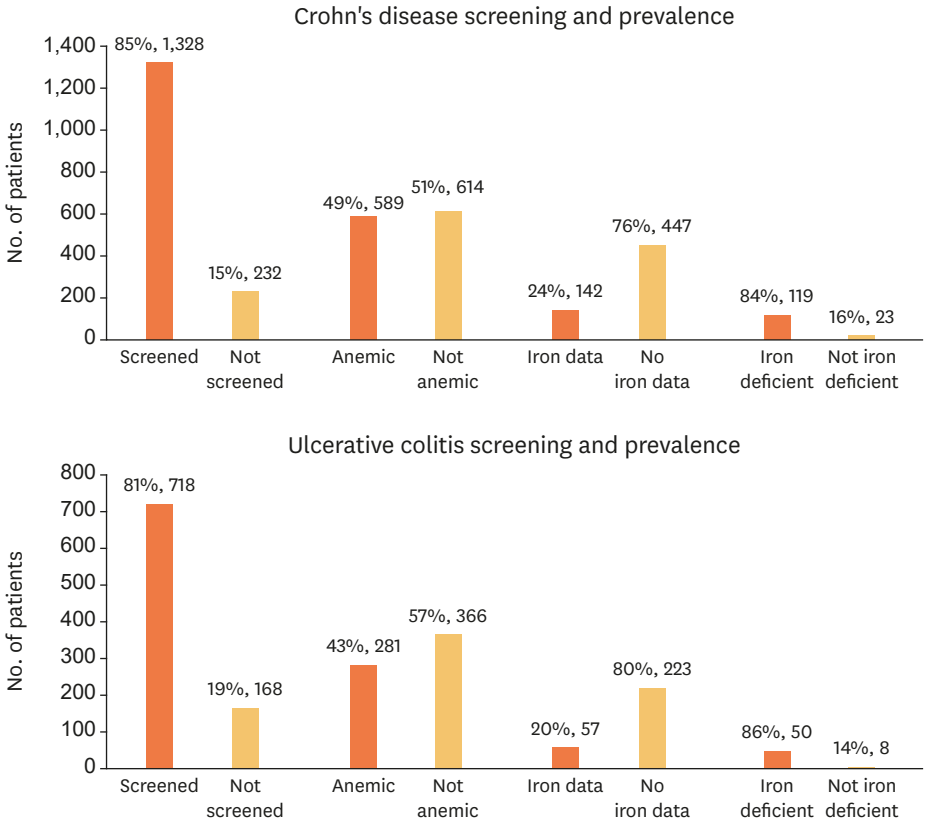

Fig. 1. Prevalence of screening, anemia and iron deficiency anemia among children with IBD. Results are presented here of the % and number of patients who were screened for anemia with % rounded to 0 decimal places. The number of screened patients was used to determine the % of patients with anemia. The number of anemic patients was used to determine the % of patients with lab evaluation for iron deficiency. The number of patients with sufficient iron data was used to determine the % of iron deficient patients.
IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis.

deficiency anemia. Of this screened sample, iron deficiency anemia was present in 84% of CD patients and 86% of UC patients (**Fig. 1**).

Prevalence of treatment by anemia status

Among patients with CD, 5% (n=81) were administered iron, while 4% (n=39) of UC patients were given iron. Only 1% of CD and 1% of UC patients received oral iron. Among patients with anemia, 8% of both CD and UC patients received IV iron. Among patients with iron deficiency anemia, 13% of CD patients and 20% of UC patients received IV iron (**Supplementary Fig. 2**). Female children with CD were treated more often than males, however, there was no difference in treatment by sex with UC. There were no age differences in treatment (**Table 3**).

Examination of the unscreened cohort

Among patients with CD, 15% were never screened, while 19% of UC were never screened. Among unscreened patients, the age and sex distribution were similar to the rest of the cohort. In unscreened patients with CD, 49% had <10 outpatient visits. For unscreened patients with UC, 70% had <10 visits. Unscreened patients with CD were treated with biologics (31%), immunomodulators (27%), and steroids (41%) compared to 40%, 44%, and 55% among those screened. This pattern was similar for patients with UC (**Supplementary Table 2**).

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DISCUSSION

This is the first study to look at prevalence of anemia screening in a population of children with IBD, and as such has direct implications for current practice. At least 80% pediatric patients with either CD or UC were screened. Females with UC were screened less often than males and adolescents aged 14–21 were screened less often than children aged 12–13. Adolescent age and female gender may therefore be potential targets for quality improvement. Examination of the unscreened cohort revealed other potential clinical variables that require a more in-depth investigation including number of outpatient visits and treatment with IBD medications. It may be possible that some members of the unscreened cohort had less severe disease requiring less frequent screening, but this hypothesis requires further investigation.

Screening for iron deficiency among patients with anemia was quite low (1 in 5 IBD patients). ECCO guidelines recommend at least annual screening for iron deficiency with ferritin and screening every 3 months for patients with anemia [7]. This is another potential target for quality improvement, especially given the very high prevalence of iron deficiency among those who were tested.

The overall prevalence of anemia in this population is consistent with many of the prior single-center studies (**Table 1**). The robustness of this estimate across study designs suggests that nearly half of children with IBD are likely to benefit from iron therapy. The higher prevalence of anemia among patients with elevated CRP as opposed to normal CRP is also consistent with prior studies [3,4,8,9], though further research is needed to explore which marker of disease activity is most clearly associated with development of anemia.

Compared with prior studies that looked at anemia treatment in children with IBD, prevalence of oral iron supplementation was overall much lower in this cohort, however MarketScan only includes prescription data and does not include over the counter utilization. Treatment with IV iron was similar to prior studies, especially those with laboratory-confirmed anemia, of whom about 8% were treated in our study (**Table 1**).

There are several weaknesses in the data source upon which this study was based. Some demographic factors could not be determined from the data including patient race, patient socioeconomic status, subspecialty of the treating physician, and practice setting (e.g., academic vs. community). The potentially important sub-population of patients on Medicaid could not be examined in this cohort as MarketScan only includes privately insured patient data. Inpatient lab results could not be determined. We attempted to account for the lack of inpatient labs by presuming that patients were screened for anemia during inpatient encounters, which would over-estimate prevalence of screening. To limit this overestimation, we required that at least one outpatient lab result (related to anemia or otherwise) was available per child.

In summary, screening for anemia and diagnosis of anemia are common among children with IBD but screening for iron-deficiency anemia and iron treatment are not. Quality improvement initiatives might increase screening for iron-deficiency anemia among children with laboratory evidence for anemia and treatment with IV iron among children with active disease. This paper reconfirms the high prevalence of anemia among children with IBD, and raises the possibility of use of process markers such as rates of anemia screening and

treatment as quality indicators. Increasing adherence to the process measures for screening and treatment of anemia may lead to improved outcomes for pediatric IBD.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Minimum hemoglobin and hematocrit levels used to define anemia in people living at sea level

Click here to view

Supplementary Table 2

Demographic characteristics of unscreened cohort

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Supplementary Fig. 1

Inclusion criteria for pediatric CD and UC patients in MarketScan®, 2010–2014. Inclusion and exclusion criteria used to define the cohort are reported with numbers of remaining patients provided at each stage of exclusion, represented as “n=”.

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Supplementary Fig. 2

Prevalence of Fe treatment among all patients, screened, anemic, and Fe deficiency anemic children with IBD. Anemia treatment by screening, anemia status, and Fe deficiency status. Results are presented here of the % and number of patients with CD in the upper graph and UC in the lower graph who were treated with Fe with % being rounded to 0 decimal places. The leftmost columns use the entire cohort as the denominator. The next set of columns uses screened patients as the denominator. The next set of columns uses patients with anemia as the denominator. The rightmost set of columns uses patients with Fe deficiency as the denominator.

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