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ORIGINAL ARTICLE

Improving Anemia in Inflammatory Bowel Disease: Impact of the Anemia Care Pathway

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Abstract

Background Anemia is a common complication of inflammatory bowel disease (IBD). Despite existing guidelines for anemia in IBD, it is frequently under-treated and the prevalence of anemia has remained high. To address this gap, the Crohn's and Colitis Foundation developed the Anemia Care Pathway (ACP).

Aims To implement the ACP in a managed care setting and identify where it improves practice habits and where barriers remain.

Methods The ACP was implemented from July 2016 through June 2017 and retrospectively studied. Run charts were used to identify shifts in iron deficiency screening and treatment as well as anemia prevalence. Results were compared to those of other providers in the same center not using the ACP.

Results 640 IBD encounters were studied. In the ACP clinic ($n=213$), anemics received iron therapy in only 30% of encounters at baseline but improved to 80%. Concurrently, anemia prevalence decreased from 48 to 25%. Screening for iron deficiency, however, did not improve. No shifts were seen in the non-ACP clinics ($n=427$) across the same period despite awareness of the ACP and other guidelines.

Conclusions Across 1 year, we observed gaps in the screening and treatment of anemia in IBD. Although screening rates did not improve, the ACP appeared to reduce missed opportunities for iron therapy by about half. Most importantly, this was associated with an overall decrease in anemia prevalence. Future refinements to the ACP should be focused on enhanced screening and follow-up.

Keywords Anemia · Iron therapy · Iron deficiency · Inflammatory bowel disease · Anemia care pathway

Introduction

Anemia is the most common extra-intestinal complication of inflammatory bowel disease (IBD) both at diagnosis and during flare ups, with prevalence between 20 and 68% [1–5].

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Despite the long history of anemia in IBD, it remains under-recognized and under-treated [1–5]. Anemia is associated with higher rates of hospitalization, prolonged hospital courses, and disturbed quality of life with reduced ability to work, chronic fatigue, and impaired cognitive function [6–9]. Anemia has also been linked to increased mortality and health care costs [10, 11]. These associations are not unique to anemia in IBD and have been reported in myriad other chronic illnesses including cancer, infection, autoimmune disease, renal disease, and chronic heart failure [12, 13].

In IBD, the etiology of anemia is multifactorial, resulting from chronic intestinal blood loss, impaired iron absorption, and anemia of inflammation (previously known as anemia of chronic disease) [14]. This leads to imbalances in iron homeostasis, and multiple studies have demonstrated that these imbalances are the most common reason for anemia in IBD [14–18]. Accordingly, iron deficiency has become an independent treatment target in IBD, even without the presence of anemia [14].

However, across practices many gaps remain in addressing and treating iron deficiency anemia (IDA) in IBD. These gaps occur across the spectrum of clinical care, from recognition to treatment and follow-up [19]. This arises due to a lack of standardized screening and follow-up protocols, an inconsistent definition of iron deficiency in IBD, and a frequent perception that the management of anemia falls second to that of IBD disease activity. Even when anemia is recognized, providers have variations in their thresholds for treatment and their comfort levels with prescribing oral or parenteral iron [19].

In recognition of these issues, in 2007, Gasche et al. developed the first set of guidelines defining anemia in IBD. They created screening parameters and addressed iron supplementation for the treatment of anemia [20]. In 2015, Dignass et al. developed the European guidelines and further expanded on the screening, workup, and treatment of IDA in IBD. Despite these efforts, there remains significant variation in provider perceptions and management of anemia. In 2016, the anemia care pathway (ACP) was developed to further address these inconsistencies in clinical practice [19]. Clinical care pathways involve multidisciplinary development and take guidelines a step further by translating them into an explicit algorithm for daily practice. This includes detailing each step in the course of treatment, defining thresholds precisely, and specifying exact timeframes for monitoring [21]. Clinical care pathways used in postoperative settings have improved discharge outcomes and reduced costs [22–24]. The purpose of this study is to test the implementation of the ACP in a managed care setting with the goal of improving rates of iron therapy in anemic patients, reducing the prevalence of anemia, and identifying barriers to ACP implementation.

Methods

Study Design

The ACP was implemented using the Model for Improvement and Plan-Do-Study-Act (PDSA) cycles in the Michael E. DeBakey VA Medical Center IBD clinic starting in July 2016 [25]. ACP implementation was performed in a staged fashion with implementation starting with one provider to assess patient and provider barriers prior to spread to other providers. All providers were aware of the ACP but did not actively participate in PDSA cycles to implement the ACP. Key ACP implementation components included patient education, and integration of anemia screening reminders in the electronic note templates.

Anemia Care Pathway (ACP)

The ACP was implemented on July 1, 2016, as described in prior publication [19]. Screening was performed with hemoglobin (Hb) and iron studies for anemia (males Hb < 13.0 g/dL, and females Hb < 12 g/dL) or iron deficiency (ferritin < 30 ng/mL). The goal was to screen Hb in all patients in the ACP clinic. Patients identified as having deficiencies of either vitamin B12 (< 211 ng/ml) or folate (< 7 ng/ml) were excluded from the analysis. Among anemic patients, inadequate iron stores were defined as ferritin < 100 ng/mL or ferritin > 100 ng/mL with transferrin saturation < 20%. Patients with anemia and inadequate iron stores with clinical, endoscopic, or radiographic evidence of inflammation were recommended to have parenteral iron; patients without evidence of active inflammation were recommended to have oral iron supplementation unless they reported current or prior intolerance to oral iron. Iron overload states (ferritin > 800 ng/mL) led to a hematology referral while adequate iron stores (ferritin > 100 ng/mL and transferrin saturation > 20%) led to assessment for other causes of anemia such as medication side effects, vitamin B12 deficiency, and folate deficiency. A 1-month follow-up was performed to look for an increase in hemoglobin (Hb) of at least 2 g/dL from baseline. If the response was inadequate, therapy was escalated or the patient was referred to hematology. If the response was adequate, a repeat Hb follow-up was performed at 2 months. If the anemia failed to resolve, therapy was escalated or the patient was referred to hematology. If the Hb was above the World Health Organization (WHO) cutoffs and there was no persistent fatigue, the patient continued to receive routine Hb screening and symptomatic monitoring at future appointments.

Data Collection

Data were collected via a retrospective audit of the electronic medical record from July 1, 2016 to June 30, 2017 using a standardized data extraction form. Demographic data included age, gender, and race. Clinical data included IBD therapy, Montreal Classification, and laboratory values. IBD medications were classified as 5-aminosalicylate derivatives (5-ASA), steroids (prednisone, budesonide), thiopurines (azathioprine and 6-mercaptopurine), methotrexate, and biologics (tumor necrosis factor- α inhibitors [infliximab, adalimumab, certolizumab, and golimumab], vedolizumab, and ustekinumab). Biologics were recorded as current therapy if they were given at the time of the encounter or within 3 months prior. IBD-related surgeries were documented if they occurred at any point prior to the encounter. IBD phenotype was classified according to the Montreal Classification [26].

Laboratory values for anemia included Hb, ferritin, iron, and transferrin saturation as the closest value within 3 months of a clinic encounter. Iron therapy was considered current if the patient was prescribed oral iron or had received a parenteral iron infusion within 3 months prior to a clinic encounter. Iron therapy was considered as past therapy if it was more than 3 months prior to a clinic encounter.

Data Analysis

The primary endpoints were (1) the prevalence of anemia and (2) the prevalence of anemic patients prescribed iron therapy. These were calculated on a monthly basis across the 12-month study period. Changes over time were analyzed using run charts, a quality improvement tool supported by the Institute of Healthcare Improvement (IHI) [27]. Using run charts, outcomes over time were compared to the pre-intervention baseline and improvements in the post-intervention trend were deemed significant when a "shift" occurred. With run charts, this has been defined as six or more data points (months) consecutively deviating in the same direction away from the baseline (i.e. either all above or all below the baseline). The baseline was defined by the median of the first 3 months (July–September). The run chart analysis was performed for the ACP clinic as the primary analysis. It was repeated for the non-ACP clinic for supplemental comparison.

Interrupted time series (ITS) analysis was performed as an exploratory outcome. ITS provides a more robust statistical analysis but typically requires a larger sample size to be adequately powered.

Demographic and clinical characteristics were also analyzed to identify if any were associated with anemia. The paired *t* test was used for continuous variables with a normal distribution and the Wilcoxon rank sum test for nonparametric variables. For categorical variables, Fisher's exact test was used.

Results

Patients and Baseline Characteristics

A total of 265 unique patients were seen in the IBD clinic during the study period. Thirteen were B12 or folate deficient and were excluded. This left a total of 252 unique IBD patients (100 in the ACP clinic and 152 in the non-ACP clinics), comprising 640 IBD encounters (213 in the ACP clinic and 427 in the non-ACP clinics). Overall, the mean (± SD) age of the patients at first encounter during the study period was 52.1 ± 15.2 years. 87.7% were male and 60.7% were Caucasian. Characteristics were largely similar between the ACP and non-ACP clinics with the exceptions of age (mean 48.6 vs. 54.5 respectively, $p = 0.002$), 5-ASA use (37% vs. 58%, $p = 0.002$), and age of onset for Montreal Classification of ulcerative colitis (Fisher's exact test, $p = 0.001$) (Table 1).

Run Charts

Anemia Prevalence

In the ACP clinic, the baseline prevalence of anemia was 47.6%, as defined by the median from July to September 2016. The median prevalence of anemia decreased to 25% in the post-implementation period (Oct 2016 to June 2017). On run chart analysis, this decrease resulted in a significant downward shift with nine consecutive time points below the baseline median ($p < 0.05$) (Fig. 1). Conversely, over the same period, the non-ACP clinics demonstrated no significant changes in anemia prevalence from its baseline of 20% (Fig. 1). For the ACP clinic, the run chart analysis was supplemented with an exploratory interrupted time series analysis. This attributed the ACP with a 19.4% decrease in the prevalence of anemia ($p = 0.067$; Supplemental Figure 1).

Rates of Iron Therapy Among Patients with Anemia

In the ACP clinic, the baseline prevalence of iron therapy among anemic patients was 30%. Three months after ACP implementation (month six), the percentage of anemic patients being prescribed iron therapy rose to a median of 80%. On run chart analysis, this corresponded to a significant upward shift with six consecutive points above the baseline ($p < 0.05$) (Fig. 2). When this analysis was repeated with an interrupted time series analysis using month six as the intervention time point, the ACP was attributed with a 62% increase in anemics receiving iron therapy ($p = 0.001$, Supplemental Figure 2). In the non-ACP clinics, run charts

Table 1 Demographic and clinical characteristics of the patients at first encounter

Characteristic	ACP clinic ($n=100$)	Non-ACP clinic ($n=152$)	P value
Demographic			
Age—year ± SD	**48.6 ± 14.3**	**54.5 ± 15.4**	**0.002**
Male sex—no. (%)	89 (89%)	132 (87%)	0.753
Race or ethnic group—no. (%)			0.372
White	65 (65%)	88 (58%)	
Black	32 (32%)	50 (33%)	
Hispanic	2 (2%)	10 (7%)	
Asian	0 (0%)	2 (1%)	
Other	1 (1%)	2 (1%)	
Clinical			
IBD-related surgery	30 (30%)	38 (26%)	0.525
IBD therapy—no. (%)			
5-ASA	**37 (37%)**	**88 (58%)**	**0.002**
Steroids	20 (20%)	22 (14%)	0.260
Thiopurine	24 (24%)	26 (17%)	0.238
MTX	4 (4%)	4 (3%)	0.716
Anti-TNF	36 (36%)	37 (24%)	0.064
Vedolizumab	4 (4%)	2 (1%)	0.218
Montreal classification			
Ulcerative colitis	$n=43$ (43%)	$n=80$ (53%)	0.147*
Age of onset—no./total no. (%)			**0.001**
A1 (< 16 years)	0/43 (0%)	1/80 (1%)	
A2 (17–40)	34/43 (79%)	36/80 (45%)	
A3 (> 40)	9/43 (21%)	43/80 (54%)	
Extent—no./total no. (%)			0.134
E1 (proctosigmoiditis)	1/43 (2%)	12/80 (15%)	
E2 (left-sided)	7/43 (16%)	9/80 (11%)	
E3 (pancolitis)	32/43 (74%)	52/80 (65%)	
Unknown	3/43 (7%)	7/80 (9%)	
Crohn's disease	$n=53$ (53%)	$n=62$ (41%)	
Age of onset—no./total no. (%)			0.359
A1 (< 16 year)	2/53 (4%)	1/62 (2%)	
A2 (17–40)	34/53 (64%)	33/62 (53%)	
A3 (> 40)	17/53 (32%)	28/62 (45%)	
Localization—no./total no. (%)			0.782
L1 (ileal)	12/53 (23%)	10/62 (16%)	
L2 (colonic)	10/53 (19%)	12/62 (19%)	
L3 (ileocolonic)	30/53 (57%)	37/62 (60%)	
L4 (isolated upper)	1/53 (2%)	1/62 (2%)	
Unknown	0/53 (0%)	2/62 (3%)	
Behavior—no./total no. (%)			0.750
B1 (non-stricturing, non-penetrating)	21/53 (40%)	31/62 (50%)	
B2 (stricturing)	16/53 (30%)	16/62 (26%)	
B3 (penetrating)	11/53 (21%)	10/62 (16%)	
B4 (penetrating, stricturing)	5/53 (9%)	5/62 (8%)	
Perianal involvement—no./total no. (%)	15/53 (28%)	10/62 (16%)	0.177

Bold values are statistically significant ($P < 0.05$)

ACP Anemia care pathway, *SD* standard deviation, *no.* number, *5-ASA* 5-aminosalicylic acid, *MTX* methotrexate, *anti-TNF* anti-tumor necrosis factor

*p value for distribution of IBD diagnoses (ulcerative colitis vs. Crohn's disease vs. IBD-unknown)

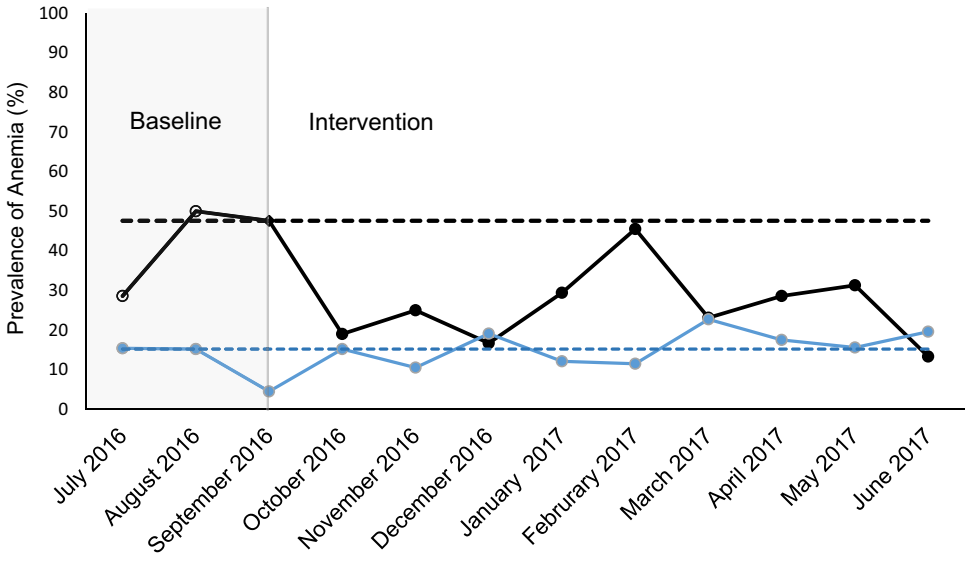

Fig. 1 Run chart for anemia prevalence over time. The baseline prevalence for each clinic (dotted lines) was defined by the median of the first 3 months. In the ACP clinic (black), a shift toward decreased prevalence was observed with nine consecutive points below baseline. The baseline median was 47.6% and improved to 25% from September 2016 to June 2017 ($p < 0.05$). No shifts were seen in the clinics without ACP implementation (blue)

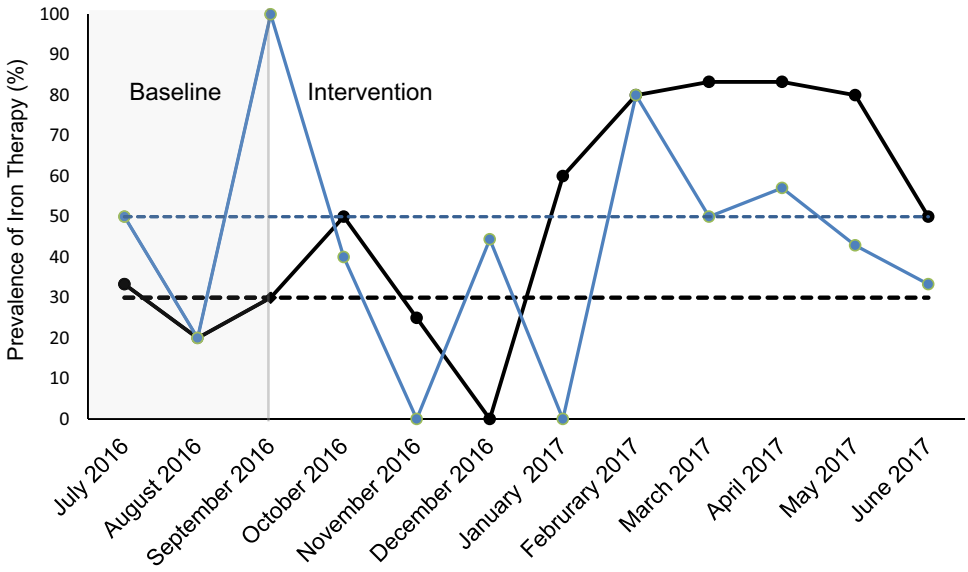

Fig. 2 Run chart for prevalence of iron therapy over time. The baseline prevalence for each clinic (dotted lines) was defined by the median of the first 3 months. In the ACP clinic (black), the prevalence of iron therapy showed a positive shift with six consecutive data points above baseline in the last 6 months. The initial median was 30% and improved to 80% from January to June 2017 ($p < 0.05$). No shifts were seen in the clinics without ACP implementation (blue)

revealed that there were no shifts in the prevalence of iron therapy over the same period (Fig. 2). No patients reported worsening of IBD activity with oral iron supplementation (no increases in stool output, bloody stools, abdominal discomfort, nausea, or emesis).

Screening for Anemia and Iron Deficiency

At baseline in the ACP clinic, 100% of patients were screened with Hb but only 20% with ferritin. At baseline in the non-ACP clinics, 53% of patients were screened with Hb and 4% with ferritin. After ACP implementation, follow-up data did not show a shift in any of these screening rates from their respective baselines.

IBD-Related Predictors of Anemia

The association of anemia with patient demographic and IBD factors was examined, including with past or current IBD therapy, age, gender, IBD phenotype and past IBD surgery. Past IBD surgery was associated with current anemia ($p = 0.016$) (Table 2). Other factors were not associated with anemia.

Barriers to ACP Implementation

As anticipated, several barriers to implementation of the ACP were observed. Improvements were tied to increasing treatment rates of patients who were identified as anemic; however, rates of complete screening were unchanged. One

Table 2 Associations between patient characteristics and anemia

Characteristic	Anemic ($n=47$)	Not anemic ($n=136$)	P value
Demographic			
Age—year ± SD	51.5 ± 15.9	53.4 ± 15.2	0.473
Male sex—no. (%)	40 (85%)	122 (90%)	0.557
Race or ethnic group—no. (%)			0.264
White	26 (55%)	88 (65%)	
Black	20 (43%)	41 (30%)	
Hispanic	0 (0%)	5 (4%)	
Asian	1 (2%)	1 (1%)	
Other	0 (0%)	1 (1%)	
Clinical			
Iron therapy—no. (%)			
Received in past	4 (9%)	7 (6%)	0.477
IBD therapy—no. (%)			
IBD-related surgery	19 (41%)	29 (22%)	**0.016**
5-ASA	20 (43%)	67 (49%)	0.532
Steroids	10 (21%)	25 (18%)	0.826
Thiopurine	13 (28%)	29 (21%)	0.491
MTX	4 (9%)	3 (2%)	0.073
Anti-TNF	20 (43%)	38 (28%)	0.094
Vedolizumab	3 (6%)	2 (1%)	0.108
IBD type—no. (%)			0.492
Ulcerative colitis	21 (40%)	68 (50%)	
Crohn's disease	23 (54%)	64 (47%)	
IBD-unknown	3 (6%)	4 (3%)	

Bold value is statistically significant ($P < 0.05$)

no. number, *SD* standard deviation, *5-ASA* 5-aminosalicylic acid, *MTX* methotrexate, *anti-TNF* anti-tumor necrosis factor

barrier was the lack of a formal system to track patients with incomplete screening, screened positive for anemia, or needed iron infusions. Laboratory results were typically ordered after the point-of-care visit, and therefore when a low hemoglobin was detected, follow-up of additional screening laboratories was frequently delayed until the next scheduled visit as many patients did not return to clinic solely for follow-up laboratories.

Discussion

In this study, we demonstrated that implementation of the ACP in an IBD managed care setting was associated with increased rates of iron supplementation among anemic patients and a reduction in the prevalence of anemia. This was demonstrated using run charts, a validated tool for quality improvement analyses. Changes in the post-intervention trend were deemed significant when they met criteria for a "shift." This was defined by having at least six consecutive data points deviated in the same direction away from the pre-intervention baseline, either all above or all below. Analyses show that the probability of a shift approximates an alpha level of 0.05 [27]. To supplement this, a more robust analysis was attempted with an interrupted time series model. This showed a trend toward improved anemia prevalence, but it was not statistically significant (decrease of 19.4%, $p=0.067$). This was likely due to limited sample size given that this study was designed for run chart analyses and was underpowered for ITSA.

Improvements were also seen in the rates of iron supplementation for anemic patients. Run charts showed a significant improvement in the prevalence of iron therapy after ACP implementation, with an increase from a median of 30% at baseline to 80% in the final 6 months. Again, since at least six data points were above the baseline median, this was deemed a significant post-intervention shift corresponding to $p<0.05$. The interrupted time series model for this data also showed a significant shift, attributing the ACP with a 62% increase in iron therapy with $p=0.001$, however only after accounting for a delayed intervention onset at month six. The delayed improvement in this trend was likely due to the long follow-up period between appointments wherein patients were often not started on iron until

their next follow-up. This finding highlights the importance of either acquiring screening laboratories before a clinic visit or ensuring follow-up of laboratories soon after. This level of detail is not addressed by the ACP yet remains a barrier to timely treatment.

The ACP was created despite pre-existing guidelines on the management of anemia in IBD because prior studies have shown that simple awareness of guidelines does not result in substantive changes in practice. This was again demonstrated in the non-ACP clinics, where providers were aware of anemia guidelines but did not strictly implement them. In those clinics, no shifts in anemia treatment nor prevalence were observed over the study period, despite being in the same facility as the ACP clinic.

The ACP clinic still showed shortcomings, however. Although Hb was screened in 100% of encounters at baseline, rates of screening for ferritin were low (20%) and did not increase after ACP implementation. Observed barriers to identifying iron deficiency frequently involved difficulty with acquiring follow-up iron studies after a patient was identified as anemic. The barrier was twofold in that it (1) required the clinic to identify and reach out to patients who were identified as anemic after the appointment, and (2) relied on the patient to return to clinic for a laboratory draw, which they were often reluctant to do. This resulted in many iron panels being delayed until the next clinic appointment or lack of follow-up altogether. Similar to our experience, Patel et al. have shown that 33% of patients with ulcerative colitis and anemia have not been tested for IDA; and among those tested and diagnosed with IDA, 25% are not treated with iron replacement therapy [16]. In the ACP clinic, this was eventually addressed by universally screening patients with an iron panel; however, the yield and cost-effectiveness of this approach will need to be determined. An automated reminder system for patients and providers for when to follow up laboratories could aide timeliness of re-evaluation after iron therapy to see if additional therapy or escalation is required. Population management tools to identify all anemic patients would address a major barrier to efficient follow-up and initiation of therapy. Patient follow-up on laboratories may also be more effective if screening laboratories are drawn prior to an appointment.

Our study had a number of limitations. While rules for detecting significant shifts in a run chart are validated for guiding quality improvement interventions, they do not provide traditional statistics such as effect sizes and confidence intervals. We supplemented the significance of the run chart findings by showing that the improvements were only seen in the clinic where the ACP was implemented. Since a positive trend was not seen concurrently in the non-ACP clinics, this suggested that the improvements in the ACP clinic could be attributed to the ACP. This conclusion, however, is partially confounded by differences between the clinics' baseline characteristics. Chief among these is that the ACP clinic had a higher baseline prevalence of anemia and therefore more room to improve. The two clinics also differed in that there was a significantly higher use of 5-ASA in the non-ACP providers, as well as trends toward higher prevalence of biologic use in the ACP clinic. These differences may be reflective of patients with more severe disease in the ACP clinic. Still, the results of the ACP clinic's run chart analyses stand on their own by design. They do not rely on comparison with the non-ACP clinics. The ACP clinic's control and experimental groups are derived internally from the pre-intervention and post-intervention trends, respectively.

In general, the 12-month study period may have also been inadequate to capture all improvements generated by the ACP. Patients were usually scheduled for follow-up every 3–12 months depending on their current therapy and hence may not have followed up during the study period if their initial appointment was in the latter half of the study period. Finally, we have only shown the ACP implemented in a single provider's clinic. This introduces bias toward a single provider's ability to adapt to changing clinical practice, baseline understanding of iron deficiency in IBD, and comfort with prescribing parenteral and oral iron therapy. Future analyses with multi-provider implementation would help to minimize these biases.

Conclusion

We demonstrated that ACP implementation resulted in significant improvements in our two primary endpoints—increased administration of iron therapy to anemic patients and decreased prevalence of anemia. These encouraging results emphasize the potential for care pathways to effectively improve management practices and outcomes. However, even at the end of the study period there was still a substantial prevalence of anemia and patients who remained unscreened. Future studies should evaluate the spread of ACP to multi-provider settings and the use of population management tools with longer follow-up to assess the clinical impact of the ACP.

Author's contribution JKH contributed to study design, data analysis, and authorship of manuscript. He has approved of the final draft submitted; TQ contributed to authorship, data analysis, and editorial input of the manuscript. He has approved of the final draft submitted; TPN contributed to authorship, data analysis, and editorial input in the manuscript. He has approved of the final draft submitted. RW contributed to editorial input in the manuscript. He has approved of the final draft submitted. DW contributed to editorial input in the manuscript. She has approved of the final draft submitted. RS contributed to editorial input in the manuscript. He has approved of the final draft submitted.

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Compliance with ethical standards

Conflict of interest JH has served as a speaker for Abbvie, Janssen, served as a consultant for Pfizer, Janssen, Daichii Sankyo, and Abbvie. JH has received research funding from Abbvie, Janssen, Pfizer, Celgene, Eli-Lilly, and Redhill Biopharma. TQ, TN, RW, DW, RS have no financial disclosures.

Ethical considerations The institutional review boards of the Baylor College of Medicine and Michael E. DeBakey VA Medical Center in Houston, Texas, approved this study.

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