# Variation in Treatment of Patients with Inflammatory Bowel Diseases at Major US Referral Centers

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## Abstract

We performed a prospective study of patients with inflammatory bowel diseases to examine variations in treatment among medical centers. In a prospective cohort study of 1659 patients with CD and 946 patients with UC seen at 7 high-volume referral centers, we collected data on demographics, disease characteristic, and medical and surgical treatments. We used logistic regression to determine differences in treatment among centers, controlling for potential confounders. We found significant variations among centers in treatment of CD with immunomodulators (odds ratio [OR], 3.34; 95% confidence interval [CI], 2.09 – 5.32) but not anti-tumor necrosis factor agents (OR, 1.64; 95% CI, 0.97 – 2.77). There was less variation in

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treatment of UC; we found no difference in use of immunomodulators (OR,1.83 95% CI, 1.00 – 3.36) or anti-TNF therapy (OR, 0.81; 95% CI, 0.40 – 1.65). Development and implementation of evidence-based standards of care for IBD may help reduce variation and improve outcomes.

## Keywords

Sinai Helmsley Alliance for Research Excellence (SHARE) consortium; IBD; practice variation; anti-TNF agent

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) (inflammatory bowel diseases, IBD) affect 1.5 million individuals in the United States.[1] Despite important advances in understanding its biology, the lack of standardized phenotyping, large enough cohort sizes, and detailed biospecimen repositories have impeded progress in targeted treatment options. To overcome these barriers, investigators from seven major IBD centers formed the Sinai Helmsley Alliance for Research Excellence (SHARE) in 2010 to integrate information from basic science, epidemiology and information sciences to advance IBD research across multiple high-volume centers. The consortium provides a unique opportunity to examine between-center practice variation in the management of CD and UC, a particularly pertinent question in view of significant recent changes in the treatment paradigms.

With the expansion of the therapeutic options available for the management of IBD, there has been a move towards the earlier use of biologic therapy and combination treatment.[2, 3] Yet, this wide range of treatments and management protocols introduces the possibility of significant variation in practice and outcomes. Few studies have examined such differences previously.[4-7] Identification of such variations is an important first step in examining its impact on outcomes which, in turn, could lead to standardizing management algorithms to deliver uniformly high quality of care. In this study, we hypothesized that there would be variation in the use of biologics and immunosuppressive agents in the management of CD and UC despite enrollment of patients from high-volume referral centers.

## METHODS

SHARE is a consortium of IBD researchers at seven academic medical institutions with high-volume IBD practices utilizing a shared protocol for prospective recruitment, and phenotyping, biospecimen collection. Recruitment began in January 2012 and is ongoing. Adult patients (18 years or older) with a confirmed diagnosis of IBD validated by chart review are eligible. Eligibility was initially restricted to patients diagnosed with IBD within the past 4 years, but subsequently relaxed to include all patients. Baseline surveys were administered within 30 days of the initial consent and included information on demographics, disease characteristics, and current and past treatment history. Disease location, behavior, or extent was classified according to the Montreal classification.[8]

We examined between-center variation in practice for CD and for UC. First, we examined the unadjusted frequency of current use of agents within each therapeutic class across each

study site. To adjust for the difference in patient characteristics, multivariate logistic regression analysis was performed with the site with the lowest unadjusted frequency as the reference stratum, adjusting for age at diagnosis, disease duration, gender, race, disease behavior, location or extent and smoking status. We also examined the likelihood of patients at each site currently on combination treatment with an immunomodulator and anti-TNF biologic, or immunomodulator naive. We repeated the analysis among patients who were within 4 years of diagnosis. Exploratory analysis was stratified by disease behavior, location or extent. To exclude the effect of a single site being an outlier, we compared the difference in practice between the extreme centers with the median values and excluded the center with the lowest frequency of utilization of each therapy by repeating our models. All analyses were performed using Stata 12.0 (StataCorp, College Station, TX). Statistical significance was defined as $p < 0.05$. The Institutional Review Boards at each participating institution approved the study.

## RESULTS

At the end of February 2014, our cohort included 2,690 total participants (1,659 CD, 946 UC, 60 with indeterminate colitis(IC)). The median duration of disease was 4 years (interquartile range 2-13 years). Table 1 describes the patient characteristics.

Current use of oral 5-ASA was seen in 30% of CD patients (range 13-46%) with fourfold variation between centers with the highest and lowest frequency of use (odds ratio (OR) 4.28, 95% confidence interval (CI) 1.29 – 14.27) (Table 2). Striking variations were similarly observed in current use of immunomodulators (range 16% - 56%, $p < 0.001$) and anti-TNF therapy (range 31% - 60%, $p < 0.001$). The difference between the centers with extreme frequencies was not explained by differences in disease characteristics and remained significant in our multivariate analysis for immunomodulator use (OR 3.34, 95% CI 2.09 – 5.32) but not anti-TNF biologics (OR 1.64, 95% CI 0.97 – 2.77). The proportion of patients on combination immunosuppression ranged from 8% to 32% (OR 3.15, 95% CI 1.79 – 5.56). There was also significant variation in proportion of immunomodulator-aive patients who started on anti-TNF biologics (range 10 – 17%) (OR 2.09, 95% CI 1.16 – 3.77). The variation across centers was not restricted to medical treatments alone. The proportion of CD patients undergoing at least one surgery ranged from 32% to 55% (OR 2.24, 95% CI 1.28 – 3.92).

The variation in practice was less in UC than CD. We observed a slight difference in the current use of oral aminosalicylates (range 48-71%, adjusted OR 2.83, 95% CI 1.08 – 7.50) but no difference in use of immunomodulator (OR 1.83, 95% CI 1.00 – 3.36) or anti-TNF therapy (OR 0.81, 95% CI 0.40 – 1.65). However, there were significant variations in the use of topical therapy, steroids, and proportion of patients undergoing surgery (Table 2).

The likelihood of use of biologics or combination immunosuppression did not inversely correlate with increased likelihood of surgery. The findings remained largely consistent when the analysis was restricted to patients diagnosed within 4 years of study enrollment. Similar results were obtained upon excluding the site with the lowest frequency for each parameter.

## DISCUSSION

Since the pioneering work by Wennberg,[9-11] numerous studies have reported variation in practice. This initial analysis of a prospective multi-center IBD cohort showed two-four fold variation in frequency of use of various medications for both CD and UC. In addition, we also identified significant variations in use of recently modified treatment paradigms.

Practice variation is important because of its potential impact on cost, utilization and patient outcomes. However, there has been limited exploration of such practice variation in the management of IBD. Several studies have demonstrated that for complex IBD surgery, having the procedure at a high-volume hospital is associated with better outcomes.[4-6] In a Canadian study, in-hospital gastroenterologist care was associated with lower mortality.[12] Benchimol *et al*. found a significant variation in prescription of various medications between different countries.[7] Kappelman *et al*. observed significant variation in the use of immunomodulators, steroids, aminosalicylates and infliximab in newly diagnosed CD across 10 academic pediatric gastroenterology centers, [13] consistent with our findings in adult IBD care. The differences in treatment that remain significant, despite adjusting for severity of disease, suggests that other explanations underlie this variation.

It is also interesting to note that variation was less overall for UC than CD. Possible explanations include greater heterogeneity in the natural history and likelihood of progression of CD thus a greater menu of therapeutic options for CD, and wider debate in the literature about the need for early aggressive therapy and modified therapeutic paradigms. With the expansion of options for treatment of UC, it is possible that we will see more variation in the management of UC. Also, surgery for UC is often considered curative[14] while the surgical treatment of CD is often followed by recurrence and requires re-initiation of treatment.[15, 16]

There are several pertinent implications for our findings. Variation in treatment generally occurs when there is uncertainty about the best practice. It is possible that the variation will diminish as evidence on effective IBD therapy grows and evidence-based guidelines become available and are implemented.[17-20] The continued variation suggests that there is significant potential for standardization of care across referral and community practices. Variations observed between the different sites may not be solely due to providers at these referral centers, but also a reflection of the practice of referring physicians and patient expectations, and differences in the insurance environments influencing prescribing behavior. Future studies must explore the sources of such variation in practices in order to appropriately target interventions. An important first step that will be achieved through continued follow-up of patients enrolled within this consortium will be to examine the consequence of such variations.

We acknowledge several limitations within our analyses. As noted above, the variation observed may also reflect, in part, the practices of the referring community at each of the sites and the proportion of new patients. However, we do not believe that those factors explain the findings for the following reasons. First, as examining between-center variation was not the *a priori* aim of this consortium, it is unlikely that there is a systematic bias in

recruiting and our findings remained on adjustment for disease severity. Our results were also not driven by a single outlier as the center with the lowest (or highest) frequency of use of a particular therapy was not always the same for each parameter examined. Second, as endpoints like new medical and surgical therapy was not frequent enough during follow-up, we were not able to examine the impact of variation in practice on subsequent outcomes. Third, patients were not recruited consecutively and may not be generalizable to all patients seen at the centers.

In conclusion, we describe the development of a multi-institution consortium that allowed for demonstration of significant practice-variation between high-volume IBD centers. Development and implementation of evidence-based standards of care may reduce variation and improve patient outcomes. As adherence to guidelines is frequently inadequate, reduction of practice variation also requires continual improvement, including setting goals and repeated measurement of processes in order to identify how standardizing care impacts outcomes.

## ACKNOWLEDEMENTS

## REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012; 142:46–54. [PubMed: 22001864]

2. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 362:1383–95. [PubMed: 20393175]

3. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008; 371:660–7. [PubMed: 18295023]

4. Ananthakrishnan AN, McGinley EL, Binion DG. Does it matter where you are hospitalized for inflammatory bowel disease? A nationwide analysis of hospital volume. Am J Gastroenterol. 2008; 103:2789–98. [PubMed: 18684184]

5. Kaplan GG, McCarthy EP, Ayanian JZ, et al. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterology. 2008; 134:680–7. [PubMed: 18242604]

6. Nguyen GC, Nugent Z, Shaw S, et al. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. Gastroenterology. 2011; 141:90–7. [PubMed: 21458455]

7. Benchimol EI, Cook SF, Erichsen R, et al. International variation in medication prescription rates among elderly patients with inflammatory bowel disease. J Crohns Colitis. 2013; 7:878–89. [PubMed: 23018106]

8. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006; 55:749–53. [PubMed: 16698746]

9. Perrin JM, Homer CJ, Berwick DM, et al. Variations in rates of hospitalization of children in three urban communities. N Engl J Med. 1989; 320:1183–7. [PubMed: 2710191]

10. Wennberg JE. Forty years of unwarranted variation--and still counting. Health Policy. 2014; 114:1–2. [PubMed: 24373550]

11. Wennberg JE, Freeman JL, Shelton RM, et al. Hospital use and mortality among Medicare beneficiaries in Boston and New Haven. N Engl J Med. 1989; 321:1168–73. [PubMed: 2677726]

12. Murthy SK, Steinhart AH, Tinmouth J, et al. Impact of gastroenterologist care on health outcomes of hospitalised ulcerative colitis patients. Gut. 2012; 61:1410–6. [PubMed: 22684482]

13. Kappelman MD, Bousvaros A, Hyams J, et al. Intercenter variation in initial management of children with Crohn's disease. Inflamm Bowel Dis. 2007; 13:890–5. [PubMed: 17286275]

14. Bernstein CN, Ng SC, Lakatos PL, et al. A review of mortality and surgery in ulcerative colitis: milestones of the seriousness of the disease. Inflamm Bowel Dis. 2013; 19:2001–10. [PubMed: 23624887]

15. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. Br J Surg. 2000; 87:1697–701. [PubMed: 11122187]

16. Buisson A, Chevaux JB, Bommelaer G, et al. Diagnosis, prevention and treatment of postoperative Crohn's disease recurrence. Dig Liver Dis. 2012; 44:453–60. [PubMed: 22265329]

17. Clark M, Colombel JF, Feagan BC, et al. American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21-23, 2006. Gastroenterology. 2007; 133:312–39. [PubMed: 17631151]

18. Dassopoulos T, Sultan S, Falck-Ytter YT, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013; 145:1464–78. [PubMed: 24267475]

19. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011; 60:571–607. [PubMed: 21464096]

20. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response? Am J Gastroenterol. 2011; 106:199–212. [PubMed: 21045814]

**Table 1**

Characteristics of the study population

| Characteristics | | Number | % |
|---|---|---|---|
| **Sex** | *Female* | 1,379 | 52.4 |
| | *Male* | 1,251 | 47.6 |
| **Age (in years)** | *18-24* | 429 | 16.0 |
| | *25-34* | 831 | 31.0 |
| | *35-44* | 537 | 20.0 |
| | *45-55* | 403 | 15.0 |
| | *55+* | 482 | 18.0 |
| **Race/Ethnicity** | *Asian* | 64 | 2.6 |
| | *Black* | 121 | 4.9 |
| | *White* | 2178 | 88.0 |
| | *Other/Unknown* | 112 | 4.5 |
| **Smoking** | *Ever* | 718 | 30.4 |
| **Current diagnosis** | *Crohn's Disease* | 1659 | 61.9 |
| | *Ulcerative Colitis* | 946 | 35.3 |
| | *Indeterminate Colitis* | 75 | 2.8 |
| **Disease Location (CD)** | *Terminal ileum* | 405 | 24.2 |
| | *Colon* | 322 | 19.2 |
| | *Ileocolonic* | 825 | 49.3 |
| **Disease Behavior (CD)** | *Inflammatory* | 736 | 43.9 |
| | *Stricturing* | 418 | 25.0 |
| | *Penetrating* | 402 | 24.0 |
| **Perianal fistula (CD)** | | 144 | 16.6 |
| **Disease Extent (UC)** | *Ulcerative proctitis* | 104 | 10.2 |
| | *Left sided* | 284 | 27.9 |
| | *Extensive disease* | 499 | 49.0 |
| **Disease Duration (in years) [Median (IQR)]** | | 4 (2-13) | |

IQR – interquartile range

**Table 2**

Between-center variation in the management of Crohn's disease and Ulcerative colitis

| Current Use | Entire cohort (%) | Site with lowest frequency (%) | Site with highest frequency (%) | Adjusted OR (95% CI) (highest vs. lowest) |
|---|---|---|---|---|
| **Crohn's disease** | | | | |
| Oral 5-ASA use | 30 | 13 | 46 | 4.12 (1.26 – 13.49) |
| Immunomodulator use [+] | 38 | 16 | 56 | 3.34 (2.09 – 5.32) |
| Corticosteroid use [+] | 15 | 7 | 21 | 2.23 (1.09 – 4.56) |
| Anti-TNF use[+] | 47 | 31 | 60 | 1.64 (0.97 – 2.77) |
| Combination IMM-anti-TNF therapy [+] | 21 | 8 | 32 | 3.15 (1.79 – 5.56) |
| IMM naive TNF-use[+] | 12 | 10 | 17 | 2.09 (1.16 – 3.77) |
| Ever surgery[+] | 44 | 32 | 55 | 2.24 (1.28 – 3.92) |
| **Ulcerative colitis** | | | | |
| Oral 5-ASA use | 58 | 48 | 71 | 2.83 (1.08 – 7.50) |
| Topical therapy (5-ASA or steroids) | 52 | 42 | 77 | 4.50 (1.40 – 14.43) |
| Immunomodulator use [+] | 17 | 7 | 25 | 2.32 (1.05 – 5.13) |
| Corticosteroid use [+] | 30 | 18 | 44 | 1.83 (1.00 – 3.36) |
| Anti-TNF use | 23 | 20 | 30 | 0.81 (0.40 – 1.65) |
| Combination IMM-anti-TNF therapy IMM naive TNF-use Ever surgery[+] | 9 9 14 | 6 6 9 | 13 15 25 | 1.14 (0.48 – 2.78) 1.46 (0.60 – 3.52) 4.45 (1.72 – 11.53) |

ASA – aminosalicylates, IMM – immunomodulator (azathioprine, 6-mercaptopurine, methotrexate), Anti-TNF – antibodies to tumor necrosis factor (infliximab, adalimumab, certolizumab pegol)

[+] p <0.05 across the different sites

CD multivariate models adjusted for disease behavior, location, age at diagnosis, disease duration, smoking status, sex, and race UC multivariate models adjusted for disease extent, age at diagnosis, disease duration, smoking status, sex, and race