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ORIGINAL ARTICLE

Is Modern Medical Management Changing Ultimate Patient Outcomes in Inflammatory Bowel Disease?

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Abstract
Background The impact of modern medical management of inflammatory bowel disease (IBD) on surgical necessity and outcomes remains unclear. We hypothesized that surgery rates have decreased while outcomes have worsened due to operating on "sicker" patients since the introduction of biologic medications.
Methods The Nationwide Inpatient Sample and ICD-9-CM codes were used to identify inpatient admissions for Crohn's disease and ulcerative colitis. Trends in IBD nutrition, surgeries, and postoperative complications were determined.
Results There were 191,743 admissions for IBD during the study period. Surgery rates were largely unchanged over the study period, ranging from 9 to 12 % of admissions in both Crohn's disease and ulcerative colitis. The rate of poor nutrition increased by 67 % in ulcerative colitis and by 83 % in Crohn's disease. Rates of postoperative anastomotic leak (10.2–13.9 %) were unchanged over the years. Postoperative infection rates decreased by 17 % in Crohn's disease (18 % in 2003 to 15 % in 2012; $P < 0.001$) but did not show a trend in any direction in ulcerative colitis.
Conclusions Rates of IBD surgery have remained stable while postoperative infectious complications have remained stable or decreased since the implementation of biologic therapies. We identified an increase in poor nutrition in surgical patients.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Surgery

Background

Medical management of inflammatory bowel disease (IBD) is constantly evolving to achieve the goal of avoiding surgery, maintaining remission, and potentially achieving a cure. The medication armamentarium has expanded in the last decade with the approval and widespread use of biologic medications for both Crohn's disease (CD) and ulcerative colitis (UC). While many have achieved remission and long-term maintenance with the use of these agents, a number of studies have called into question their long-term efficacy.[1–3] Despite the known limitations, physicians and patients continue to hold out hope for remission on biologic treatments, often trialing a series of agents over several years before referral to a surgeon. This is a natural response, as surgery is an unpalatable option for many, particularly CD patients in whom surgery is not curative.

What remains unclear about current medical management of IBD is the ultimate impact on surgical necessity. While epidemiologic data suggests that CD surgery rates have been steadily decreasing in the modern era,[4,5] at least 15–30 % of UC patients and half of CD patients will still require surgery.[3,4,6] Because many IBD patients require surgery despite "maximized medical therapy," it is important to understand of the impact of current IBD management on both surgical outcomes and overall patient health.

Limited data exist to answer these questions. Nevertheless, it seems clear from recent reports that there is a trend in UC

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patients away from up-front total proctocolectomy and toward total abdominal colectomy with a staged completion proctectomy.[6] This trend in and of itself has been interpreted as an indication that UC patients are now arriving to the surgeon in a "sicker" state than they were in the past. Unfortunately, no direct evidence exists regarding the overall health of these patients when they present after failing all medical options.

While still controversial, slightly more evidence exists regarding postoperative complications in patients who received preoperative biologic medications. Unfortunately, the data is mixed and largely of fairly poor quality. Most of the studies have failed to show any association between biologic medications and postoperative infectious complications in either CD or UC, although enough evidence to the contrary exists to drive continued debate.[7–14]

The long-term impact of modern medical management on IBD surgery rates, postoperative outcomes, and overall patient health remains in question. We therefore used a large, validated, national database in order to address these issues. We specifically sought to assess nutrition status, surgical rates, and postoperative outcomes among IBD patients in the decade since the introduction of biologic medications. We hypothesized that surgery rates have decreased while malnutrition and postoperative complications have increased due to operating on sicker patients since the introduction of biologic medications.

Materials and Methods

This is a nationwide, retrospective review of all IBD patients admitted from 2003 to 2012 as reported to the Nationwide Inpatient Sample (NIS). Approval was obtained from our local Institutional Review Board. The NIS is composed of de-identified HIPAA-compliant data from over 1000 hospitals and over 8,000,000 admissions annually across the USA. The data is gathered and submitted by Health Care Cost and Utilization Project (HCUP) partners, which are state data organizations that have partnered with the Agency for Healthcare Research and Quality (AHRQ). It provides information on primary and secondary diagnoses, primary and secondary procedures, and patient demographics (e.g., gender, age). We investigated demographics, diagnoses, and surgical procedures in all patients who were admitted with a primary ICD-9 diagnosis of either CD (555.0, 555.1, 555.2, or 555.9) or UC (556.0–556.9) during the study period. The main outcomes of interest were the presence of a surgical procedure, the nutritional status of the patients at the time of surgery, and postoperative infectious complications. These outcomes were trended over the 10 study years.

ICD-9 codes were used to identify surgical procedures, patient comorbidities, and postoperative complications. Specific procedures of interest included total abdominal colectomy (TAC) (45.8) with or without ileorectal anastomosis (IRA) (45.92), total proctocolectomy (TPC) (defined as patients who had a code for both TAC and proctectomy) (48.40–48.43, 48.5, 48.50–48.52, 48.59, 48.61–48.65, 48.69) with or without ileostomy (46.01, 46.2, 46.20–46.23), small bowel resection (45.6), and segmental colectomy (45.7). These procedures were chosen as they are known surgical options for IBD and in some cases (such as TPC) may tell us something about the patient's health at the time of operation. Stoma creation or primary anastomosis was not analyzed separately, as the rationale for diversion is multifactorial and may reflect surgeon or patient preference rather than the true condition of the patient. Furthermore, approximately one in three ileostomies were coded as unspecified, making it difficult to determine the true rates of end vs. loop ileostomies. Analyzed comorbidities included active smoking (649.0, 305.1), obesity (278.00, 278.01), and malnutrition (abnormal loss of weight and underweight (783.2), unspecified protein-calorie malnutrition (648.9), other and unspecified protein-calorie malnutrition (263), nutritional marasmus (261), or other severe protein-calorie malnutrition (262)). Postoperative complications included anastomotic leak (997.49) and overall postoperative infection (sepsis (998.02), urinary tract infection (997.5), wound infection (998.30–998.33), and other postoperative infection (998.51, 998.59)).

The number of admissions for each year was determined, and the trend over the years was analyzed using simple weighted linear regression. Similarly, mean age at surgery, rates of poor nutrition, rates of surgical procedures, and rates of postoperative complications were trended over time using linear regression analysis. Statistical analysis was performed using PASW Statistics 22.0.0 (SPSS Inc., Chicago, IL), and significance was set at $P < 0.05$.

Results

Out of 191,743 admissions for IBD during the study period, 120,044 were for CD and 71,699 were for UC. CD admissions increased from 11,360 to 12,593, while UC admissions increased from 6803 to 7235 over the study years ($P < 0.001$) (Fig. 1). Non-elective admission rates for CD and UC increased (79 and 76 to 85 and 82 %, respectively; $P < 0.001$), while non-elective surgery rates decreased (40 and 33 to 38 and 27 %, respectively; $P < 0.001$) (Fig. 2). The admission to surgery ratio for both CD and UC varied between 6 and 12 %. There was a statistically significant difference in CD admission to surgery rates over the study years ($P < 0.001$), while there was no such difference among UC patients ($P = 0.87$) (Fig. 3). Neither disease process demonstrated a consistent trend over time. The average age of CD and UC patients at

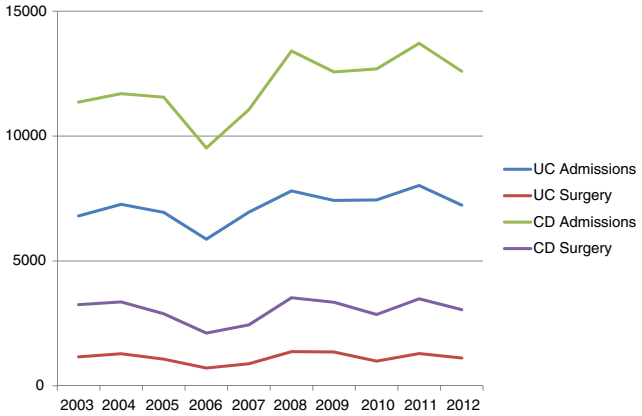

Fig. 1 Admissions and surgeries for patients with inflammatory bowel disease between 2003 and 2012

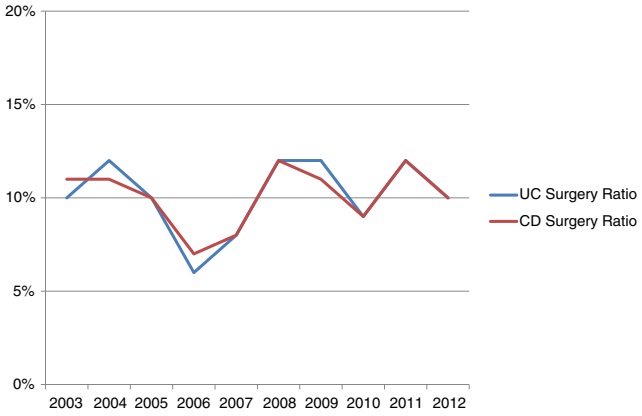

Fig. 3 Ratio of inflammatory bowel disease admissions to surgeries between 2003 and 2012

the time of surgery decreased from 43 to 41 years and 46 to 44 years, respectively ($P < 0.001$) (Fig. 4).

The rate of malnutrition among CD patients undergoing surgery increased by 83 % (8.6 % in 2003 vs. 14.9 % in 2012; $P < 0.001$) over the study period. Surgical UC patients followed a similar trend, with a 67 % increase in malnutrition (9.3 % in 2003 vs. 15.4 % in 2012; $P < 0.001$). The obesity rates for both CD and UC patients undergoing surgery also steadily increased over the study period (2 to 6 % for CD and 4 to 9 % for UC; $P < 0.001$). The rate of smoking in surgical CD increased from 8 % in 2003 to 12 % in 2012 ($P < 0.001$). There was no significant difference in the smoking rate in surgical UC over the years (3 % in 2003 to 4 % in 2012; $P = 0.39$) (Figs. 5 and 6).

Of the operations for CD, 32,684 were performed between 2003 and 2012. This included 7932 (24 %) TACs, 3989 (12 %) TPCs, 5380 (16 %) small bowel resections, and 15,383 (47 %) segmental large bowel resections (including ileocecectomies). While the rates of each procedure were slightly different from year to year ($P < 0.001$), there was no clinically significant change in the trend (Fig. 7).

UC patients underwent 12,424 procedures between 2003 and 2012. These included 6569 (53 %) total abdominal colectomies (with or without delayed pouch reconstruction), 3423 (28 %) total proctocolectomies (with or without pouch reconstruction), 384 (3 %) small bowel resections, and 2048 (16 %) segmental large bowel resections. As with CD, UC surgeries had statistically significant differences in rates of surgery from year to year ($P < 0.001$). We noted a 13 % decrease in single-stage proctocolectomy over time (31 % in 2003 to 27 % in 2012; $P < 0.001$); however, no other procedures had a clinically significant trend over the study years (Fig. 8).

The rates of overall infectious complications in the decade examined were 17.5 and 17.9 % in CD and UC, respectively. Anastomotic leak rates ranged between 10 and 14 % for surgical CD patients with no significant difference between years ($P = 0.23$). Overall postoperative infection rates for CD patients decreased by 17 % (18 % in 2003 to 15 % in 2012; $P < 0.001$) over the study period (Fig. 9). Rates of anastomotic leak in surgical UC patients ranged from 8 to 13 % with no statistically significant difference between years ($P = 0.13$). UC postoperative infection rates ranged from 14 to 21 % ($P < 0.001$) with no particular directional trend over the years (Fig. 10).

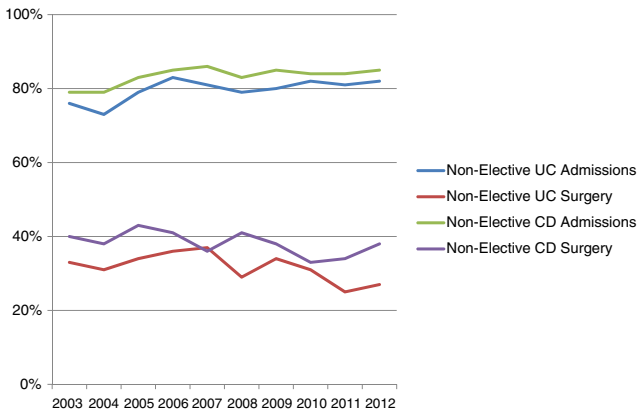

Fig. 2 Non-elective admissions and surgeries for patients with inflammatory bowel disease between 2003 and 2012

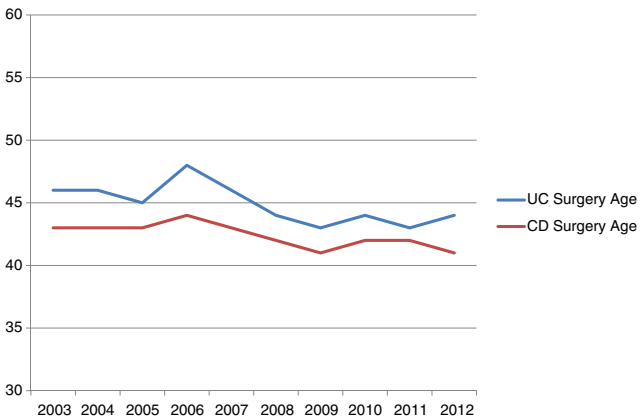

Fig. 4 Mean age (years) of inflammatory bowel disease patients undergoing surgery between 2003 and 2012

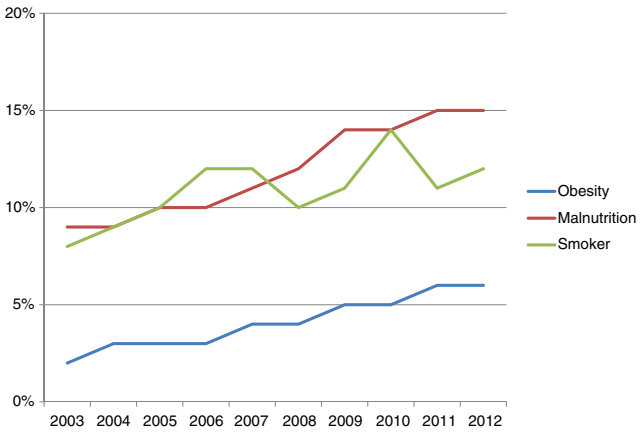

Fig. 5 Obesity, malnutrition, and smoking rates in Crohn's disease patients undergoing surgery between 2003 and 2012

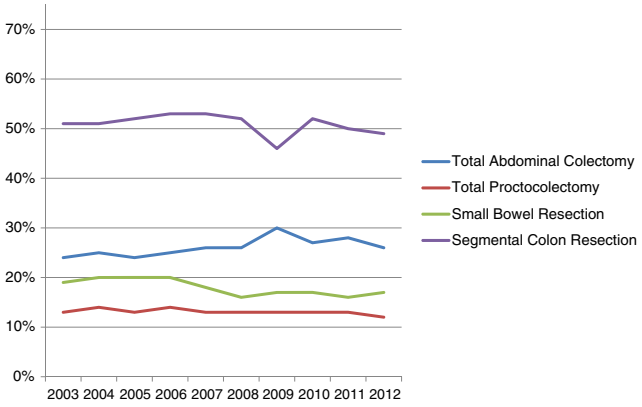

Fig. 7 Rates of specific procedures in surgical Crohn's disease patients between 2003 and 2012

Discussion

We used a large national database to assess demographics, nutrition status, rates of surgery, and postoperative outcomes among IBD patients in the decade since the introduction of biologic medications. Overall admissions and non-elective IBD admission rates trended up over the years, while rates of non-elective IBD surgery decreased. The overall rate of surgical necessity did not follow any particular trend. We did, however, find that the average age for surgery trended downward (younger) in both the CD and UC groups. We also found disturbing and consistent increases in malnutrition, obesity, and smoking rates in surgical IBD patients. The types and frequency of surgical procedures remained fairly constant over the study period, the one exception being total proctocolectomy rates, which steadily downtrended. Rates of anastomotic leak did not change over time. Overall postoperative infectious complications downtrended in CD and did not show a consistent trend in either direction in UC.

Inflammatory bowel disease is generally felt to be due to autoimmune dysfunction in the gastrointestinal tract. As such, a number of immune-modulating medications have been trialed over the years with some success. The latest addition to the IBD medication armamentarium is so-called biologic therapy. Infliximab was the first widely utilized biologic used in IBD and was approved for CD in 1998 and for UC in 2005. While biologics have shown efficacy in inducing remission, reducing symptoms, and promoting mucosal healing,[1·3·15·16] there has been a persistent population of IBD patients who are either medically refractory from the onset or who become so with time.[2] Furthermore, at least 15–30 % of UC patients and at least half of CD patients will require surgery.[3·4·6] Recent studies have suggested that approximately 30 % of IBD patients undergoing surgery have trialed biologic therapy.[9] It is therefore important to understand the impact of failed medical management on patient physiology and surgical prognosis.

Epidemiologic data suggest that CD surgery rates have been steadily decreasing since the introduction of immune-modulating agents and have continued to decline in the era of biologics.[4·5] A similar trend has been seen with UC, where relatively small randomized controlled trials have shown a significant decrease in early colectomy rates among UC patients started on infliximab.[17·18] Despite these favorable trends, series with long-term follow-up have questioned this beneficial effect in chronic, refractory UC.[2] Additionally, the

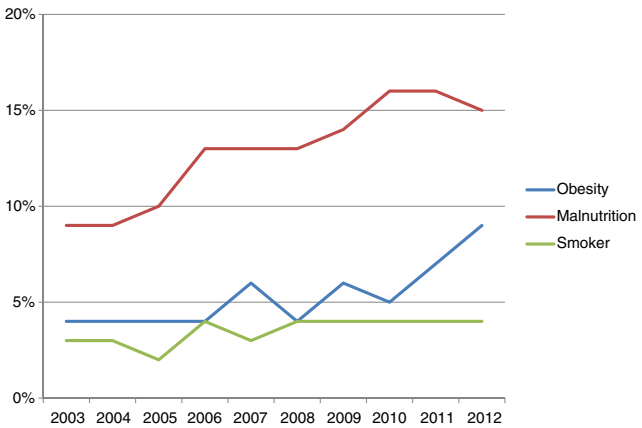

Fig. 6 Obesity, malnutrition, and smoking rates in ulcerative colitis patients undergoing surgery between 2003 and 2012

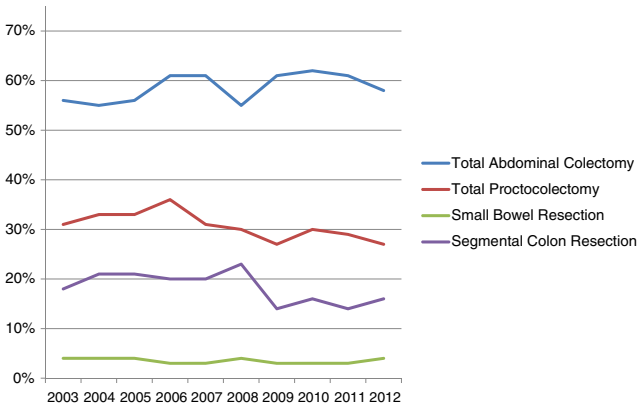

Fig. 8 Rates of specific procedures in surgical ulcerative colitis patients between 2003 and 2012

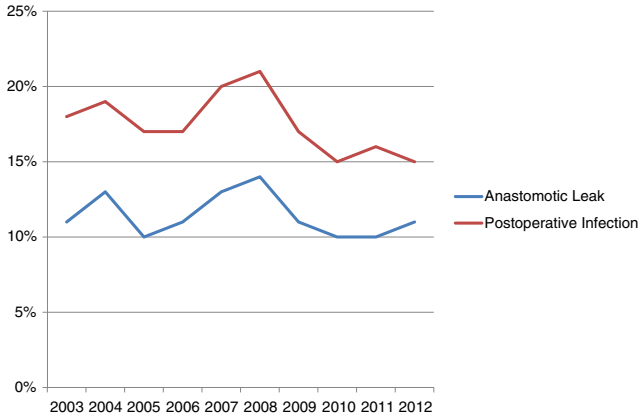

Fig. 9 Postoperative complication rates in Crohn's disease patients between 2003 and 2012

mere fact that IBD surgery rates were on the decline before the development of biologic therapy in and of itself calls into question the ultimate necessity of these medications. The current study indicates that IBD admissions have increased over the last decade despite modern medical management. The rate of surgical necessity in patients requiring admission has not changed substantially, ranging from 6 to 12 % of IBD admissions. This compares favorably to population-based studies which place the 5-year risk of first CD surgery at 18 %.[5] It should be noted, however, that the average age of surgical patients decreased over the study years, which perhaps argues against studies suggesting decreases in early surgery with modern management. Nonetheless, the decreasing rate of non-elective surgery for IBD is a promising trend and may suggest that current management allows patients time to decide for themselves when surgery is the best option.

Previous studies have found that a significant percentage of IBD patients, even when clinically well, suffer from some form of malnutrition.[19] Advances in medical management should presumably lead to improvement in the overall health of IBD patients. Surprisingly, the data presented here suggest that IBD patients are increasingly unhealthy at the time of surgery. Rates of obesity, malnutrition, and smoking have all increased substantially in this population. Whether these changes reflect selection bias, a detrimental impact of failed medical management, a change in disease phenotype, or a generational trend toward an unhealthy public cannot be determined from the present study. Overall obesity rates in the USA remained stable in people under the age of 60 during the study period (2003–2012).[20] With the mean age of our IBD cohort being approximately 45 years old, it is unlikely that a population trend can fully explain the increased obesity rates among IBD patients admitted for surgery. While our data cannot differentiate causation, it is certainly feasible that over-reliance on medication has led to a decreased emphasis on lifestyle changes, thereby leading to increased rates of smoking and obesity. Regardless of the underlying etiology, the striking rate of poor nutrition at the time of surgery cannot be ignored, as numerous studies have linked malnutrition, obesity, and smoking to adverse outcomes.[21–23] In fact, we previously identified obesity as a significant risk factor for postoperative morbidity specifically in IBD patients.[21] It is critical for us to ascertain whether modern medical management of IBD patients has caused us to push these patients to the precipice of malnourishment before a surgical referral is sought.

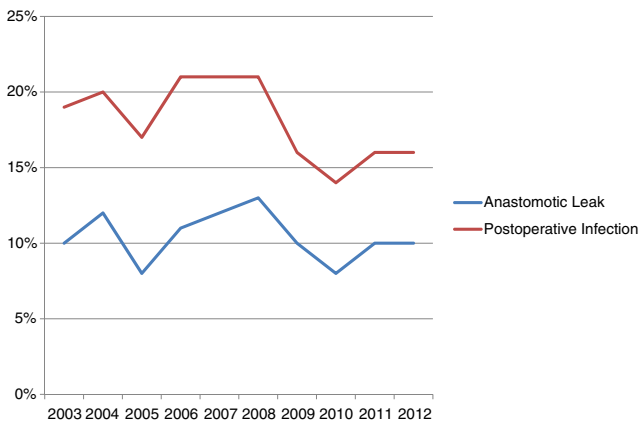

Fig. 10 Postoperative complication rates in ulcerative colitis patients between 2003 and 2012

It seems clear from recent reports that there is a trend in UC patients away from total proctocolectomy and toward total abdominal colectomy with a staged completion proctectomy.[6] The current study similarly reflects decreased rates of proctocolectomy over the decade since the introduction of biologics for UC. While rates of other procedures have not changed, the decreasing frequency of total proctocolectomy as a primary procedure has in and of itself been interpreted as an indication that UC patients are now arriving to the surgeon in a sicker state than they were in the past. The decreased rate of non-elective surgery over the study period may on the surface seem to refute this point. On the other hand, this constellation of findings (decreased one-stage proctocolectomy with decreased non-elective surgery rates) may be explained by over-reliance on medication in refractory patients, resulting in a smoldering patient who is neither healthy nor critically ill. Certainly, the rates of malnutrition identified in the current study lend credence to this interpretation. The significance of the surprisingly high rates of segmental colectomy and the presence of small bowel resections for UC is unknown. These may reflect coding errors or unexpected intraoperative findings.

A number of studies have previously addressed infectious complications in postoperative patients who have been on biologic agents.[7–14] The largest series in CD patients suggested increased rates of postoperative sepsis and abscess among those who received preoperative infliximab.[7] A more recent meta-analysis by Billioud et al. identified a significantly increased risk of infectious complications in surgical CD

patients who received preoperative anti-TNF treatment.[8] Similarly, Selvaggi et al. identified an association between preoperative biologics and early pouch-specific complications and complications after ileostomy closure in UC patients undergoing ileal pouch anal anastomosis.[9] Other studies have refuted these findings. Rizzo et al. failed to identify any increased risk of infectious complications in a mixed group of CD and UC patients undergoing surgery within 12 weeks of being on biologic therapy.[10] A meta-analysis by Yang et al. also did not identify any increased risk of postoperative infectious complications, although an association between non-infectious complications and preoperative biologic therapy was suggested in both CD and UC.[11] Ultimately, any association between modern medical management and postoperative complications is at a minimum poorly understood and perhaps even non-existent. The current study identified an overall infectious complication rate of approximately 18 % in IBD patients, which is similar to the 16 % found on meta-analysis by Billioud et al.[8] While the Billioud study suggested higher rates of infection among CD patients who received preoperative biologic agents, the current study found that overall rates of infectious complications have actually decreased among CD patients in the era of biologics. A similar finding was not observed among UC patients, who did not demonstrate any particular trend with regard to postoperative infections. It is difficult to ascertain the clinical relevance of infection rates in the IBD population. The decreased rate of infectious complications among surgical CD patients is potentially misleading, given the heterogeneity of this population. It is difficult to argue that changes in surgical management drove the decreased rates of infections in these patients, especially given that rates of different surgical procedures and anastomotic complications remained similar. The 3 % decrease in overall infections over the years can easily be explained by any number of hospital-driven initiatives to prevent urinary tract infections and hospital-acquired pneumonia. The stable rate of infectious complications in UC patients may be equally misleading, as the increasing propensity to avoid single-stage reconstruction may mask what would otherwise result in increased anastomotic complications.

This study has certain limitations. As with any retrospective database review, the analysis is limited to the documented diagnoses and procedure variables and can neither reflect the myriad of real-time factors that influence the decision-making process nor can it account for any differential reporting of diagnoses over time (i.e., malnutrition and smoking). Because there was no specific data regarding the severity of patient disease (i.e., Crohn's disease activity index), prior IBD-related abdominal surgeries, or the real-time events that occurred in the operating room (such as a decision to create a diverting stoma based on nutritional status and disease severity), it is impossible to infer what factors contributed to the decision to perform one procedure over another. As such, there are likely unrecorded confounders that may have contributed to differences seen over the years. Furthermore, the NIS itself is limited in what is recorded, as it only allows up to 15 diagnoses and 15 procedures. Undoubtedly, the most significant limitation in the current study is the inability to determine the medical management of these patients from the database. Certainly, the significance of this study rests on the assumption that the use of biologic medications for inflammatory bowel disease has increased in recent years. While we recognize the limitation of assumption, our experience is that the number of patients who have trialed these medications has increased over the last decade. Furthermore, we have evidence showing that up to 30 % of IBD patients have used biologics preoperatively[9] and that the use of biologic medications in other disease processes has increased dramatically since 2003.[24] Despite these limitations, our study represents a substantial body of data examining the epidemiology of surgical IBD in the era of biologic therapy.

Conclusions

In contrast to our hypothesis, the rate of IBD surgery has not substantially changed in the most recent decade despite modern medical management. Rates of postoperative infectious complications, to include anastomotic leak, have remained stable or decreased since the implementation of biologic therapies. We have seen a significant increase in poor nutritional status among patients who ultimately require surgery. It may be that the increased number of medications now available to the IBD patient have caused a delay in surgical consultation for non-responders, ultimately resulting in a sicker patient. Additional research is needed to determine the nature of the link between modern medical management and poor nutrition in IBD patients, as well as the overall impact on patient livelihood.

Author's Contributions Quinton Hatch: Primary investigator/author. Study conception and design, data collection and analysis, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

Rubina Ratnaparkhi: Associate investigator/author. Study conception, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

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Michael Keating: Associate investigator/author. Study conception, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

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Madhuri Nishtala: Associate investigator/author. Study conception, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

Eric Johnson: Associate investigator/author. Study conception, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

Scott R. Steele: Senior investigator/author. Study conception, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of version to be published.

Compliance with Ethical Standards

Disclaimer The results and opinions expressed in this article are those of the authors and do not reflect the opinions or official policy of the US Army or the Department of Defense.

Conflict of Interest The authors declare that they have no conflict of interest.

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