SPECIAL ARTICLE

Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colorectal Surgeons, and the American Society of Colorectal Surgeons Evidence Based Reviews in Surgery – Colorectal Surgery

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients."[1] The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and reading all of the medical literature is impossible for an individual clinician. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so they can determine the validity, reliability, credibility, and utility of individual articles, ie, critical appraisal skills. In general, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics, as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled "Evidence Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc and Ethicon Endo Surgery. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. In 2007, EBRS also included a module covering topics in colorectal surgery. Each academic year, 6 clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery, but also to cover a spectrum of methodological issues important to surgeons; for example, causation or risk factors for disease, natural history, or prognosis of disease, quantifying disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery-Colorectal Surgery (EBRS-CRS) Web site. In addition, a listserv discussion is held in which participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) can access EBRS-CRS through the Canadian Association of General Surgeons Web site (www.cags-accg.ca), the American College of Surgeons Web site (www.facs.org/education/ebrs.html), the Canadian Society of Colon and Rectal Surgeons (CSRCS) Web site (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons (ASCRS) Web site (www.fascrs.org). All journal articles and reviews are available electronically through the Web site. Surgeons who participate in the current (modules) packages can receive CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple-choice questions. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSCRS, and ASCRS Web sites or should email the administrative coordinator, Marg McKenzie at mmckenzie@mtsinai.on.ca

In addition to making the reviews available through the CAGS and the ACS Web sites, a condensed version of the reviews will be published in *Diseases of the Colon & Rectum*. We hope readers will find EBRS useful in improving their critical appraisal skills and also in keeping abreast of new developments in general surgery. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca

SELECTED ARTICLE

Jones DW, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. *Ann Surg.* 2010;252:307–312.

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OBJECTIVE: This aim of this article was to compare the use of surgical procedures for Crohn's disease before and after the introduction of infliximab.

DESIGN: This article is based on a retrospective cohort study.

DATA SOURCE: The National Inpatient Sample (NIS) was used to identify all hospital admissions for Crohn's disease for each year from 1993 to 2004. Cases of Crohn's disease and relevant surgical interventions were identified by the use of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM).

RESULTS: There was no statistically significant change in population-based rates of small-bowel and right colon resection, whereas rates of left colon resection, other colon resection, and rectal resection declined moderately. However, the rate of surgical repair of fistulas of the small intestine, the most commonly performed fistula operation, increased by 60% from 1.5 per 1,000,000 in 1993 to 2.4 per 1,000,000 in 2004 ($p = 0.04$).

CONCLUSION: During the period of adoption of infliximab as a novel treatment for Crohn's disease, overall rates of bowel resections have either remained relatively stable or decreased moderately, but the rates of small-bowel fistula repair have increased significantly. These findings call into question the effectiveness of infliximab in preventing the need for surgery for Crohn's disease at the population level.

COMMENTARY: The medical and surgical treatment of Crohn's disease in the era of infliximab is in evolution. Infliximab is a monoclonal antibody to tumor necrosis factor-alpha (TNF-α) that has been shown to enhance steroid-free remission rates at 1 year in comparison with placebo for both luminal and fistulizing Crohn's disease.[2,3] In fact, it is the first drug therapy to be proven to be effective at closing or even improving fistulas in Crohn's disease. Infliximab is costly (at least $30,000 per year in North America), so, although it is effective, whether it is cost effective remains an issue of debate. Furthermore, to what extent it has impacted on long-term outcomes such as the need for surgery is also a matter of debate. Although a well-timed operation usually leads to improved quality of life, it is not a cure, and surgery is expensive in terms of short-term direct and indirect costs. Although surgery is sometimes the first treatment option, more often it is chosen when medical therapy has failed.

Whether infliximab changes the frequency of surgical intervention for Crohn's disease is controversial; some studies have suggested fewer interventions,[4] but population-based studies have suggested no significant change in the overall rate of surgery for Crohn's disease.[5] Thus, Jones and Finlayson[6] addressed a very timely question: has the wide-spread use of infliximab affected the rate of colonic and fistula procedures in patients with a primary diagnosis of Crohn's disease?

The authors evaluated time trends in the rates of colonic and fistula procedures in patients discharged from the hospital with a primary diagnosis of Crohn's disease. The time period evaluated, 1993 to 2004, includes the date of the US Food and Drug Administration approval of infliximab for use in Crohn's disease (1998). The authors therefore evaluated secular trends in the rates of surgery for Crohn's disease, with the assumption that a change in rate after 1998 could be attributed to the use of infliximab. Data were obtained from the NIS that includes data from hospital discharges in a 20% stratified sample of US community hospitals collated yearly. The number of states represented has increased substantially over time, and hospitals from 44 states are currently included in the sample. Based on the sampling frame, nationwide estimates can be produced on a yearly basis. It is important to note, however, that the hospitals included in the sample vary yearly. In addition, there is no way to identify multiple admissions for the same patient by using these data, because each discharge is treated as an independent event.

Cases of Crohn's disease and relevant surgical interventions were identified by using ICD-9-CM codes. Each record in the NIS represents a single hospital discharge and contains many data elements unique to that hospital stay, including up to 15 distinct diagnoses and procedures. Records with ICD-9-CM codes (555.x) for Crohn's disease as primary diagnosis were included. The authors' choice of surgery codes was appropriate. Crohn's disease-specific ICD-9-CM procedure codes were used to identify a variety of surgical procedures. However, small-bowel resections (45.6x), which may be performed for either primary Crohn's disease or for fistulas from ileocolonic or colonic disease, were not included for uncertain reasons. US Census data were used to establish population denominators so that trends in population-based rates of use of these procedures were examined over time.

No attempt to measure infliximab exposure was made. Importantly, during this time period, it is unclear what proportion of patients would have been exposed to infliximab. NIS does not include these types of data, and the authors do not provide published data describing population-based rates of infliximab usage in the United States during this time period. Although evidence regarding the effectiveness of infliximab was published in 1997,[7] and the drug approved for use in 1998, guidelines for clinicians regarding the use of the drug were not published immediately,[8,9] and it is unclear when widespread usage would have occurred.

The authors found that, from 1993 to 2004, there was no statistically significant change in population-based rates of small-bowel and right colon resection, whereas rates of left colon resection, other colon resection, and rectal resection declined. However, rates of surgical repair of fistulas of the small intestine, the most commonly performed fistula operation, increased by 60%, from 1.5

per 1,000,000 in 1993 to 2.4 per 1,000,000 in 2004 ($p < 0.04$), and the authors concluded that, during the period of adoption of infliximab therapy in Crohn's disease, infliximab did not particularly impact rates of surgery for Crohn's disease .

Most trials evaluating the effectiveness of infliximab in the treatment of Crohn's disease have been performed in specialty centers, with high volumes of IBD and gastroenterologists very familiar with its use. Furthermore, only relatively short-term outcomes have been assessed. The results of these trials may not be generalizable to other centers where the indications for intervention may not be as tightly controlled and only "infliximab responders" are continued on the medication. Thus, the main strength of this study is that it is population based and that its outcomes were assessed over a longer time period, so it potentially provides a more generalizable picture of the impact of a new drug on the frequency and types of surgical interventions. However, although the findings and conclusions of this study are similar to those reported by another group exploring the same question in the NIS from 1998 to 2005,[5] there are some limitations to the study.

First, secular trends represent long-term changes in disease states. Research attempting to attribute secular trends to any particular aspects of care is prone to confounding. There were many changes in the epidemiology and management of Crohn's disease over this 12-year period, in addition to the introduction of infliximab. Importantly, a change in the prevalence of Crohn's disease may have resulted in a failure to find a reduction in surgery for Crohn's disease over time. It was assumed that the prevalence and case severity of Crohn's disease has remained stable in the population. In fact, there is evidence that the prevalence of Crohn's disease has increased over time, although whether this was significant over the short time span of this study is debatable.[10] The authors do describe a marked increase in the population-based rate of admissions with a principal diagnosis of Crohn's disease, from 182 per 1,000,000 in 1993 to 252 per 1,000,000 in 2004 (an increase of 38%) with the use of NIS data. Taken in context with an increasing rate of admissions for Crohn's disease, the failure to find an increase in the rate of surgery in the population may actually indicate a beneficial effect of infliximab. A more relevant outcome, however, would be the proportion of patients with Crohn's disease requiring surgery over time, but the authors do not present these data.

Second, data were only generated from community-based hospitals, and many IBD patients are seen in tertiary care facilities where the availability of sophisticated management techniques could refine and improve the use of infliximab (antibody level testing, ready availability of expert IBD surgeons, clinical trials for patients in whom treatment has failed). The shorter length of stay for any one admission may reflect patients being transferred to such IBD centers, but it may also account for the greater number of admissions, with overall "day count" being more consistent during the study period.

Third, the authors did not validate their definition of Crohn's disease, so it is possible that they either missed some patients with Crohn's disease who underwent surgery or counted some patients as having Crohn's disease when, in fact, they did not. In truth, this is less likely to occur in surgical studies than in studies assessing medical outcomes, because coding for Crohn's disease-related surgery is less prone to error. Nonetheless, error in identifying cases of true Crohn's disease remains a possibility.

Fourth, the benefits of sustained remission from Crohn's disease with the use of infliximab, including prevention of the need for surgical intervention, may occur only with prolonged use of the drug. The exposure window in this study may not have been sufficiently long to observe benefit biasing the study toward the null. When a new therapy is introduced we cannot expect it to impact surgery rates in Crohn's disease immediately, and perhaps the first decade is too soon to see an impact. Patients with complex or difficult to manage disease and with fibrotic strictures may come to surgery during this period because they were not candidates for this new therapy or this therapy had failed because their disease was too advanced. It may be that we need to eliminate these prevalence cases, and, when infliximab is used earlier in the disease course (as argued by some[11]), we may then start to see some impact on surgery rates. In addition, as pointed out previously, the use of infliximab post-1998 was only assumed, and the true uptake during the study period is unknown.

If we accept, however, that, in fact, Jones and Finlayson's data are truly reflecting a nationwide trend that surgery for Crohn's disease has not decreased in the past 15 years, but infliximab therapy has been on the ascent, where does this fit with what has been published on the topic?

A population-based study from Manitoba, Canada recently showed that users of infliximab did not have reduced surgery rates in comparison with new users of thiopurines or patients with Crohn's disease not using any of immunomodulators, anti-TNF-α drugs, or steroids for up to 3 years after introduction of each therapy.[12] Because anti-TNF-α therapy in Manitoba is used in a "step up" approach it may take many more years of follow-up to show a reduction in surgical rates among infliximab users. A study from the University of Chicago suggested a reduction of operations for fistulizing disease, whereas operations for luminal disease did not decrease during the era of infliximab use.[13] A study from Spain suggested that operations for both fistulizing and luminal disease decreased during the recent era of infliximab use.[14] A recent Hungarian study reported an association between early immunomodulator and biologic use with lower

rates of first surgery but not recurrent surgery.[15] Two clinical trials of anti-TNF-α therapy (one with infliximab and one with adalimumab) reported on a reduced need for surgery at 1 year in patients randomly assigned to the active drug vs those in the placebo group.[16,17] However, this effect has not been seen in recent American population-based studies, 2 of which found increasing rates of hospital admissions for Crohn's disease and no significant trends in bowel resections for the disease in the United States[18,19]; these latter studies support the conclusions by Jones and Finlayson. Because patients with Crohn's disease are using health care resources at increasing rates on a national scale, Jones and Finlayson are justified to call into question the observations reported in smaller clinical studies.[12–14]

Despite the limitations of the study, the findings are thought provoking and suggest that, despite the introduction of biologic agents, with presumably more effective and wider options for the medical management of Crohn's disease, the rate of surgical interventions has not decreased. Furthermore, the relatively indiscriminate use of infliximab as a treatment for fistulous complications of Crohn's disease may not result in long-term benefits and certainly has not avoided or decreased the need for surgery over the longer term. Rather, surgery for Crohn's disease appears to be more complex, and surgery for fistulizing Crohn's has increased, rather than decreased, with the use of infliximab. Thus, the use of infliximab for primary treatment of internal fistulas may not improve patient outcomes.

The medical and surgical management of Crohn's disease needs further study, especially in view of the overall rising costs and health care burdens associated with managing these patients. Trials comparing medical and surgical management are needed. Currently, surgery is seen as a terminal end point, when every medical option has failed. Although infliximab can be effective in the management of Crohn's disease that has not responded to other medical therapies or of patients with perianal or very extensive disease, it is expensive, and the end point of treatment is unclear. Most studies like the present one include a broad patient population that unfortunately lumps responders into the same (and much larger) group of nonresponders and assumes all will respond similarly. The key, of course, to the more effective use of any therapy is to limit its use to patients that have the highest probability of benefit. Further studies are required to identify factor(s) that predict which patients will respond to infliximab, so its use can be restricted to those patients and the cost-to-benefit ratio enhanced. Presently, there are few such indicators, but here is the great opportunity for future research in IBD management.

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REFERENCES

1. Evidence Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA.* 1992;268:2420–2425.
2. Hanauer SB, Feagan BG, Lichtensetin GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet.* 2002;359:1541–1549.
3. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med.* 2004;350:876–885.
4. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology.* 2005;128:862–869.
5. Cannom RR, Kaiser AM, Ault GT, et al. Inflammatory bowel disease in the United States from 1998 to 2005: has infliximab affected surgical rates? *Am Surg.* 2009;75:976–980.
6. Jones DW, Finlayson SRG. Trends in surgery for Crohn's disease in the era of infliximab. *Ann Surg.* 2010;252:307–312.
7. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med.* 1997;337:1029–1035.
8. Fedorak RN. Canadian Association of Gastroenterology. Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. *Can J Gastroenterol.* 2001;15:367–370.
9. Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. *Am J Gastroenterol.* 2002;97:2962–2972.
10. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis.* 2007;13:254–261.
11. 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 randomized trial. *Lancet.* 2008;371:660–667.
12. Nugent Z, Blanchard JF, Bernstein CN. A population-based study of health-care resource use among infliximab users. *Am J Gastroenterol.* 2010;105:2009–2016.

13. Rubinstein JH, Chong RY, Cohen RD. Infliximab decreases resource use among patients with Crohn's disease. *J Clin Gastroenterol.* 2002;35:151–156.
14. Saro C, De la Coba C, Casado MA, Morales JM, Otero B. Resource use in patients with Crohn's disease treated with infliximab. *Aliment Pharmacol Ther.* 2007;26:1313–1323.
15. Szamosi T, Banai J, Lakatos L, et al. Early azathioprine/biological therapy is associated with decreased risk for first surgery and delays time to surgery but not reoperation in both smokers and nonsmokers with Crohn's disease, while smoking decreases the risk of colectomy in ulcerative colitis. *Eur J Gastroenterol Hepatol.* 2010;22:872–879.
16. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol.* 2004;99: 91–96.
17. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology.* 2008;135:1493–1499.
18. Nguyen GC, Tuskey A, Dassopoulos T, et al. Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. *Inflamm Bowel Dis.* 2007;13: 1529–1535.
19. Bewtra M, Su C, Lewis JD. Trends in hospitalization rates for inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol.* 2007;5:597–601.