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, that is, critical appraisal skills. Generally, 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 Endo Surgery Inc and Ethicon Endo Surgery Canada. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. EBRS has 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 where 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 (CSCRS) Web site (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons (ASCRS) Web site (www.fascrs.org). All of the journal articles and reviews are available electronically through the Web site. Surgeons who participate in the monthly packages can receive 6 CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple-choice questions each month. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSCRS, and ASCRS Web sites or should e-mail 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 the *Diseases of the Colon & Rectum*. EBRS is useful in improving your critical appraisal skills, keeping abreast of new developments in colorectal surgery, and, most importantly, obtaining 6 CME credits each month from anywhere that you have access to a computer. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca.

SELECTED ARTICLE

Naanthakrishnan AN, Hur C, Juillerat P, et al. Strategies for the prevention of postoperative recurrence in Crohn's

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disease: results of a decision analysis. *Am J Gastroenterol.* 2011;106:2009–2017

***QUESTION*:** What is the cost effectiveness of multiple preventive medical strategies vs no therapy to prevent postoperative recurrence of Crohn's disease (CD)?

DESIGN: This was a decision tree model comparing 5 possible strategies to prevent recurrence in patients with CD who have undergone surgical resection: 1) no treatment, 2) antibiotics (ABX), 3) azathioprine (AZA), 4) upfront infliximab (IFX), and 5) tailored IFX.

SETTING: Drug costs were obtained from the 2010 Drug Topics Red Book. Hospital costs were based on previously published analysis.

PATIENTS: We included 35-year–old patients who were in surgical remission after their first ileocecal resection.

INTERVENTION: Subjects were randomly assigned to 1 of 5 strategies aimed to prevent the recurrence of CD.

MAIN OUTCOME MEASURE: The primary outcome measure was determination of the cost-effectiveness of multiple preventive medical strategies vs no therapy.

RESULTS: At the base-case analysis, the ABX (0.82 quality-adjusted life-years; QALYs) and AZA (0.81 QALYs) arms were more effective and less expensive than the no-treatment strategy (0.80 QALYs). The most effective strategy was upfront IFX (0.83 QALYs); however, this was also the most expensive and resulted in a high incremental cost-effectiveness ratio (ICER; $777,732/QALY) compared with no treatment. The tailored IFX arm was less effective than upfront use but had a more acceptable ICER. On increasing the recurrence rate to 78% (high-risk patients), upfront IFX resulted in 0.07 QALYs (ICER $130,580/QALY) gained compared with no treatment, whereas ABX, AZA, and tailored IFX arms dominated no treatment.

CONCLUSION: ABX are the most cost-effective option for preventing postoperative recurrence, but they have been associated with high rates of intolerance precluding widespread use. Upfront IFX is the most efficacious strategy but is not cost-effective even the high-risk patients. Reserving IFX use for high-risk patients with early endoscopic recurrence is the more cost-effective than upfront use in all patients.

COMMENTARY: With the evolution of medical management for CD occurring at a rapid pace, we are beginning to see a reduction in 5-year surgical rates in cohort studies that have evaluated this end point.[2] Still, surgical resection is required for many patients with CD to manage refractory symptoms and attempt to "reset the clock" by inducing remission. The majority of patients with CD who undergo ileocolic resection will develop recurrent disease, with endoscopic recurrence rates as high as 80% at 1 year, clinical recurrence rates as high as 20% to 30% at 1 year, and the need for repeat surgery as high as 65% at 10 years.[3] Given these high recurrence rates, several medical therapies, including mesalamine, nitroimidazole ABX, AZA, and IFX have been evaluated as possible prophylactic therapies in the postoperative period. For most of these agents, studies have yielded conflicting results or limiting adverse effects. Thus, the role of medical prophylaxis after surgery is not entirely clear, and clinicians have no well-defined guidelines when discussing such options with patients with CD who have undergone recent ileocolic resection.

In the study by Ananthakrishnan et al,[4] a decision analysis was performed to examine the cost-effectiveness of different postoperative prophylactic medical therapies over a 1-year time period. Five possible strategies were evaluated: 1) no treatment, 2) ABX, 3) AZA, 4) upfront IFX, and 5) tailored IFX, where treatment is based on colonoscopy findings at 6 months. A full economic evaluation requires that both costs and outcomes (QALYs) are considered. The decision tree devised by the authors outlines all of the possible clinical outcomes that were considered for these 5 treatment strategies. The probabilities used in the tree were drawn from 2 meta-analyses assessing the effectiveness of AZA and antibiotic maintenance therapy,[5,6] and 1 small, randomized controlled trial assessing the effectiveness of IFX[7] in preventing postoperative CD recurrence. The medication costs used in this study were derived from the 2010 Drug Topics Red Book (provides the costs of medication in the United States). Hospital costs for active disease, remission, and surgery were based on a previously published analysis.[8,9]

The authors compared different treatment strategies to each other by determining the extra benefit that is gained from the extra unit cost. This calculation is called the ICER. When a treatment is both less expensive and more effective, then it is referred to as a win-win situation. When this occurs there is no need to calculate an ICER. In this study, strategies were compared in an incremental cost-effectiveness analysis by creating an efficiency frontier. Strategies that were more expensive and less effective than others were considered dominated and were, thus, eliminated from the analysis. The remaining strategies were then ordered in incremental order of QALYs and costs, and ICERs were calculated in comparison with the immediately preceding strategy. Costs and QALYs were calculated for a base-case 35-year–old patient having an ileocecal resection for CD. The authors also calculated ICERs across 4 different recurrence risk strata. In the base case, the average QALY for the 5 treatment options ranged from 0.805 (for the no-treatment option) to 0.828 (for the upfront IFX option).

Although upfront IFX demonstrated the best QALY at 1 year, the ICER for this option was $2,757,857. This means that the cost for a patient who had an ileocolic resection to obtain 1 extra QALY would be in excess of $2 million. The ICERs varied depending on the risk of recurrence, ranging from $722,348 per QALY in the high-

risk group to an astounding $6,667,000 per QALY in the low-risk group.

The main reason for the large ICERs is that the differences in the average QALYs with the different treatment options were very small (range, –0.0002 to 0.2200). In this study, the authors refer to a willingness to pay a threshold of $80,000. Thus, for the most part, these ICERs are not in a range where a treatment option would be considered to be worthwhile. When the risk of clinical recurrence was estimated to be ≈10% at 1 year, AZA or antibiotic prophylaxis resulted in similar average QALYs at 1/100th the cost of IFX. When recurrence was estimated to be (unrealistically) high at 78% at 1 year, the QALY advantage of IFX is greatest, but the costs per QALY were still high at $722,348.

The authors conclude, "…antibiotics are the most cost-effective strategy to prevent postoperative recurrence. However, widespread use is precluded by high rates of intolerance and therapy cessation. Upfront IFX use is the most efficacious strategy; however, routine use is not cost effective across a wide range of recurrence rates. Tailoring IFX use to patients with high risk of recurrent disease based on risk stratification at 6 months appears to be a more cost effective approach."

The major limitation of this study is that the authors have based their decision tree on a meta-analysis derived from small, randomized controlled trials and a small clinical trial assessing the effectiveness of IFX in the postoperative setting. This limitation is mitigated by the sensitivity analysis, which suggests robust conclusions across a wide range of possible efficacies.

There are ongoing studies that may inform this analysis. The preliminary (6-month) results of the PostOperative Crohn's Endoscopic Recurrence (POCER) study, which compared adalimumab with ABX and AZA for the prevention of postoperative endoscopic recurrence, was presented at the 2012 Digestive Disease Week. All of the patients were treated initially with metronidazole for 3 months, and 93% of patients tolerated it. Patients were simultaneously treated with a thiopurine (AZA or 6-mercaptopurine) if they tolerated it or adalimumab if they did not. Of the high-risk patients in this study (smokers, perforating disease, or 2 or more resections), 62% of patients treated with a thiopurine were in endoscopic remission at 6 months compared with ≈94% of those who were treated with adalimumab. The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial comparing endoscopic recurrence rates with IFX maintenance therapy versus placebo in high-risk patients finished accruing its 475 patients in March 2012, and results are expected in 2013.

A second presentation of the POCER study presented at the 2012 Digestive Disease Week indicated that stratifying patients into high and low risk for recurrence groups was fairly accurate in predicting who would develop a recurrence. Of the low-risk patients (nonsmokers, nonperforating disease, and/or 1 resection), 73% were in endoscopic remission at 6 months with only 3 months of metronidazole as treatment compared with 60% of the high-risk patients treated with metronidazole and a thiopurine and 94% of the high-risk patients treated with metronidazole and adalimumab. Both the POCER study and the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial will better inform us of the true benefit of antitumor necrosis factor agents in the prevention of postoperative recurrence of CD.

Another limitation of this decision analysis is that it was based on data from randomized controlled trials where there was a short time frame (≤1 year), and the outcome was often endoscopic recurrence. Thus, the observed benefits may not be appreciated by the patients because the outcome may not be clinically relevant to them nor do we know whether the long-term outcome of this chronic disease is changed.

This decision analysis demonstrates that 1 size fits all is unlikely the correct approach to postoperative maintenance therapy in patients with CD. As best as we can, we need to understand how aggressive a particular patient's phenotype is to help guide medical prophylaxis options. Immediately in the postoperative period we can approach this problem by considering the patient's age, how soon after disease onset they required a resection, what medications failed previously, what the length and site of the resection was, the pathology of the surgical specimen (inflammatory, stricturing, or perforating), and the patient's smoking status. Furthermore, patient preference is important, because there is evidence that patients are reluctant to accept relatively benign medication prophylaxis when there is a clear and substantial relative risk reduction for recurrence.[10] After considering these factors and understanding the patient's preferences with regard to medical therapy, one approach might be the following: patients with an ileocolic resection should be considered for metronidazole for 1 year, although tolerance will be a limiting factor. In high-risk patients who are naive to biologics, antitumor necrosis factors agents are reasonable but costly to initiate. However, this analysis argues that the timing may be optimal after endoscopic recurrence is evident (thus avoiding overtreating certain patients). Based on the risks and benefits of AZA, which patients should be treated with this agent to prevent recurrent disease is uncertain.

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