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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for the members of the Evidence-Based Reviews in Surgery Group*

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 regarding individual patients. Medical knowledge is continually and rapidly expanding and it is impossible for an individual clinician to read all of the medical literature. 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, *i.e.*, critical appraisal skills. In general, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics, in addition to clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsored 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 was to help practicing surgeons improve their critical appraisal skills. Beginning in 2007, EBRS also included a module covering topics in colorectal surgery. Each academic year, six clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery but also because they cover a spectrum of methodologic 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 methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery–Colorectal (EBRS-CRS) website. 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 website (*www.cags-accg*), the American College of Surgeons website (*www.facs.org*), the Canadian Society of Colon and Rectal Surgeons (CSRCS) website (*www.cscrs.ca*), and The American Society of Colon and Rectal Surgeons (ASCRS) website (*www.fascrs.org*), All journal articles and reviews are available electronically through the website. 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 websites or should email the administrator, Marg McKenzie at *mmckenzie@mtsinai.on.ca*.

In addition to making the reviews available through the CAGS and the ACS websites, 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

Lobos-Alvarez M, Arostegui J, Sans M, *et al.* Crohn's disease patients carrying *Nod2/CARD 15* gene variants

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have an increased and early need for first surgery because of stricturing disease and higher rate of surgical recurrence. Ann Surg 2005;242:693–700.

QUESTION: Is the *Nod2/CARD15* gene variant an independent predictive factor for both the need for initial and subsequent surgery in patients with stricturing Crohn's disease (CD)?

DESIGN: Prospective cohort study.

SETTING: A single inflammatory bowel disease unit in Spain.

PARTICIPANTS: One hundred seventy patients with Crohn's disease (CD) (91 males, 79 females; mean age, 37.9 ± 14 years) with mean follow-up of 7.4 ± 6.1 years.

RISK FACTORS ASSESSED: *Nod2/CARD15* gene variants, gender, previous appendectomy, smoking habit, family history of inflammatory bowel disease (IBD), age at time of diagnosis of CD, location and behavior of CD, and extraintestinal manifestations of CD.

MAIN OUTCOME MEASURES: Primary outcome was abdominal surgery for stricturing CD; the secondary outcome was repeated abdominal surgery.

MAIN RESULTS: On multivariate analysis, *Nod2/CARD15* gene (odds ratio (OR), 3.58; 95 percent confidence interval (CI), 1.21–10.5) and stricturing phenotype at diagnosis of CD (OR, 9.34; 95 percent CI, 2.56–33.3) were independent predictive factors of initial surgery for stricturing lesions. Among the 70 patients that required surgery, postoperative recurrence was also more frequent in patients with *Nod2/CARD15* gene variants (OR, 3.29; 95 percent CI, 1.13–9.56) and reoperation was needed at an earlier time ($P = 0.03$).

CONCLUSION: *Nod2/CARD15* genotyping may have a useful clinical application as a major marker of evolution of CD, in particular, an early need of initial surgery because of stricturing disease and need for reoperation.

COMMENTARY: Crohn's disease is a chronic autoimmune illness characterized by intermittent inflammation of the gut that can arise from mouth to anus, and for which there is no known cure. Medical therapies are delivered with the goal of producing remittance or preventing relapse. Surgical therapies are performed with the goal of alleviating obstruction because of strictures or refractory inflammation, or managing fistula. Although the phenotypic classifications of inflammatory, stricturing, and fistulizing disease were previously thought to represent discrete categories of CD, more recently, they have been considered overlapping behaviors on a continuum. Approximately 80 percent of CD patients will require operative intervention in their lifetime, most often for strictures that cannot be treated medically. Determining the most favorable time for operation can be challenging. If operative intervention is performed before medical options are exhausted, patients may be subjected to unnecessary surgery. By contrast, if operative intervention is delayed but ultimately inevitable, surgical outcomes are compromised by the toxicity of failed medical therapies and perhaps increased postoperative complications.

To better predict which patients are most likely to require operation (by inference, those who will fail medical therapy), Alvarez-Lobos and colleagues studied a cohort of CD patients seen in a single IBD clinic. Although the genetic basis of CD susceptibility is incompletely understood, approximately 30 percent of CD patients will have a *Nod2/CARD15* gene variant. Carriers of one of the three identified polymorphisms of *Nod2/CARD15* are more likely to have terminal ileal or stricturing disease. The authors compared patients with a *Nod2/CARD15* genetic variant to those without this variant, using first-time and subsequent operations as primary and secondary outcomes.

In a 14-month period, the authors examined records of 170 adult CD patients from whom data were collected prospectively. Patients were then followed up twice yearly for a median of 5.6 years. In multivariate analysis, *Nod2/CARD15* gene variants predicted an initial abdominal operation with mutation: no mutation OR = 2.32 (95 percent CI, 1.16–4.64). That is, the odds of a patient with at least one mutation having an operation is 2.3 times the odds of a patient with no mutations having an operation. The absolute increase in risk for any first operation in a carrier of the *Nod2/CARD15* variant was 18.3 percent. That is, for every 5.4 patients with a *Nod2/CARD15* variant, there was one excess operation over the number among noncarriers.

Carriers of *Nod2/CARD15* mutations also carried a higher risk for subsequent operations. After adjusting for other clinical characteristics, patients with *Nod2/CARD15* gene variants had an increased likelihood OR = 3.18 (95 percent CI, 1.07–9.47) of a repeat operation, compared with their noncarrier counterparts. Among mutation carriers, the absolute increase in risk for a repeat operation was 29 percent. In other words, for every 3.4 patients with a *Nod2/CARD15* variant there was one excess operation compared with those without *Nod2/CARD15* mutations.

This study had several notable limitations. Most importantly, the sample size was small, prohibiting comparison of negatives, heterozygotes, and homozygotes that could have identified a "dose-response curve" and widening confidence intervals for the associations seen. Pooling data with other centers could help to clarify the results, and could go a long way toward supporting the value of genetic testing for prognostication. In addition, standard definitions for clinical data (*e.g.*, Vienna classification, Crohn's Disease Activity Index, *etc.*) were *not* used, which limits the ability to compare results with other cohorts and to generalize conclusions to other individuals. Finally, longer follow-up would have been useful for the secondary outcome because, unlike risk of colon cancer recurrence, risk of Crohn's recurrence does not decline over

time. For example, most series quote 10 to 30 percent 5-year postoperative recurrence rates (requiring a repeat operation) and 20 to 40 percent 10-year postoperative recurrence rates.

There were also several minor limitations. First, the location of the initial diagnosis was not reported. It is possible that patients whose CD was diagnosed elsewhere were actually further into the disease course or had less rigorous initial evaluation, which could compromise comparisons. Second, the authors did not report whether follow-up was complete for all patients, so conclusions must be based on the assumption that none were lost to follow-up or were otherwise unavailable. Third, relative risk (RR) would be a more appropriate measure given that operation is relatively common in this cohort, and RR reveals a weaker association between presence of a variant and first surgical intervention (unadjusted OR = 2.11, whereas unadjusted RR = 1.51).

For colorectal surgeons, these data are primarily of potential interest and are unlikely to have an immediate impact on practice. However, *Nod2/CARD15* mutation status may be useful for guiding future therapies, or identifying patients that may require more aggressive postoperative medical therapy to prevent recurrence.

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REFERENCE

1. Evidence Based Medicine Working Group. Evidence-based medicine. JAMA 1992;268:2420–5.