

Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 20.

Small gallstones may increase the risk of pancreatitis; is there a benefit for a prophylactic cholecystectomy?

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CAGS Evidence Based Reviews in Surgery

The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature, so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that clinicians 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),” which is supported by an educational grant from ETHICON and ETHICON ENDO SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson, and ETHICON INC. and ETHICON ENDO-SURGERY, INC. divisions of Johnson & Johnson Inc. The primary objective of this initiative is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the early diagnosis of disease, and the effectiveness of treatment. A methodological article is supplied that guides the reader in critical appraisal of the clinical article. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS Web site. As well, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons and the American College of Surgeons can access Evidence Based Reviews in Surgery through the Canadian Association of General Surgeons Web site (www.cags-accg.ca) or the American College of Surgeons Web site (www.facs.org). All journal articles and reviews are available electronically through the EBRS Web site. We also have a library of past articles and reviews that can be accessed at any time. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, completing the monthly online evaluation and answering the online multiple choice questionnaire. For further information about EBRS, the reader is directed to the CAGS or ACS Web site or should email the administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the CAGS and ACS Web sites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 in the *Journal of the American College of Surgeons* each year. 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 regarding EBRS may also be directed to mmckenzie@mtsinai.on.ca.

Reference

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

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Selected article

Venneman NG, Buskens E, Besselink MGH, et al. Small Gallstones are Associated with Increased Risk of Acute Pancreatitis: Potential Benefits of Prophylactic Cholecystectomy. *Am J Gastro* 2005;100(11):2540-50

Abstract

Question: Is cholecystectomy or a “wait-and-see” strategy the preferred option in patients with asymptomatic gall stones? **Design:** A Markov model with Monte Carlo simulations. **Base Case:** Patients with small (< 5 mm) asymptomatic gallstones determined by ultrasound and endoscopic retrograde cholangiopancreatography (ERCP). **Treatment alternatives:** “Wait-and-see” policy versus cholecystectomy. **Outcomes considered:** In the “wait-and-see” strategy, the individual could remain asymptomatic, develop obstructive jaundice, biliary pain, cholecystitis, pancreatitis or death from other causes. For each disease state, the patient could die or have a full recovery. In the prophylactic strategy, the patient could die postoperatively or have a full recovery. The time frame was 10 years. **Sources of estimates for probabilities and utilities:** The authors performed a retrospective review of patients at their own institution and used probabilities from the literature. Utilities for various health states were not considered. **Results:** Prophylactic cholecystectomy was shown to be of benefit only if the patient had the highest risk of developing and dying of pancreatitis (pancreatitis incidence greater than 0.15% and mortality owing to pancreatitis of 7.5% or greater). If the mortality of pancreatitis was 2.5% or 5%, life-years were actually lost rather than gained in the prophylactic cholecystectomy strategy. **Sensitivity analyses:** the effect of variable incidences and mortalities of pancreatitis were considered. **Conclusion:** Prophylactic cholecystectomy may lead to gain or

loss of life-years in patients with small stones, depending on the incidence and mortality of pancreatitis.

Commentary

Even in the era of evidence-based medicine, clinicians are faced with making decisions without evidence from randomized controlled trials. Further, decision making is often quite complex, because there may be several treatment alternatives that differ in their presumed effectiveness, their side effect and risk profile, and their disutility and cost. In addition, clinicians usually consider the individual patient’s status as well as his or her own preferences, adding to the complexity of the decision-making process. General surgeons make these types of decisions on a daily basis. For instance, is the patient with a small rectal cancer best served by having an abdominoperineal resection or a transanal excision of the lesion? Should patients with a several-day history of right lower quadrant pain and a phlegmon on CT scan undergo immediate appendectomy or be treated with antibiotics and interval appendectomy? Or, as is this month’s question, is prophylactic cholecystectomy or a wait-and-see strategy the preferred option in patients with asymptomatic gallstones?

Decision analysis is the application of explicit quantitative methods to analyze decisions under conditions of uncertainty. It allows clinicians to compare the consequences of the alternative strategies by making explicit all of the elements that need to be considered. Decision analysis can be useful in situations where there is Level I evidence supporting a treatment but there is uncertainty regarding whether it would be beneficial in an individual patient. More often, though, decision analysis is used in situations where there is no Level I evidence, and decisions must be based on lower-level evidence.

Decision analysis can be useful in assisting in decision making when

there is no obvious best treatment strategy, but its usefulness may be limited by the quality of the published evidence. They are also susceptible to bias, since a certain amount of interpretation is required by the researchers performing the analysis, especially when the evidence is poor and the reported probabilities of outcomes are variable. Sensitivity analyses are usually performed to assess the robustness of the model, but these may not eliminate this risk.

In this study, the authors performed a decision analysis to answer the posed question and conducted a retrospective review of their own experience of patients who underwent cholecystectomy at their institution between 1996 and 2002 to provide data for the decision analysis. This is somewhat unusual because it potentially limits the generalizability of the results (data from a limited number of sources are considered), and the paper is confusing.

In this decision analysis, the authors compared 2 clinical strategies: a wait-and-see policy and prophylactic cholecystectomy in patients with small (< 5 mm) asymptomatic gallbladder stones. Another possible strategy might be ERCP and prophylactic sphincterotomy. The authors did not include this as a strategy because they assumed it is associated with greater risks of dying than laparoscopic cholecystectomy (0.4% v.15%); this is not necessarily true. The quoted risk of endoscopic retrograde cholangiopancreatography (ERCP) is based on patients with various biliary problems (most notably, cholangitis/obstructive jaundice) who have a higher mortality risk than asymptomatic patients. In patients presenting with gallstone pancreatitis, endoscopic sphincterotomy may be associated with a marked reduction in the rate of recurrent pancreatitis and is considered by most to have less risk of death than laparoscopic cholecystectomy, especially in patients with significant medical comorbidities.

This article was chosen for

discussion because gallstones are being identified in increasing numbers of patients in western countries because of imaging tests performed for other reasons. As well, people with atypical abdominal pain syndromes might also have gallstones, and treatment for this group is unclear. Finally, in the current era of laparoscopic cholecystectomy, surgeons are more likely to be referred patients with asymptomatic or minimally symptomatic gallstones than in the days of traditional cholecystectomy. The current practice of not recommending prophylactic cholecystectomy in patients with asymptomatic gallstones has been based on the results of the classic study by Gracie and Ransohoff,¹ which showed that only 18% of people with asymptomatic stones developed biliary pain or a gallstone complication during the 15-year follow-up period. They also showed that the risk of cholecystectomy in asymptomatic patients was probably greater than the risks associated with ongoing observation. However, some patients with asymptomatic gallstones do become symptomatic and present with severe complications of gallstone disease. Numerous studies have attempted to determine which asymptomatic patients are at high risk for developing symptoms and complications and in whom prophylactic cholecystectomy might be indicated. To date, no specific group has been identified.

The outcomes are outlined in the model, as shown in Figure 1. The principal trade offs of the 2 strategies are the risk of death from cholecystectomy (0.15%) versus the risk of biliary complications and the need for a subsequent cholecystectomy in the wait-and-see strategy. The authors found that the number of life-years gained or lost varies, depending on the risks associated with the pancreatitis. Prophylactic cholecystectomy was shown to be of benefit only if the patient had the highest risk of developing and dying of pancreatitis (pancreatitis incidence

greater than 0.15% and mortality due to pancreatitis of 7.5% or greater). If the mortality of pancreatitis was 2.5% or 5%, life-years were actually lost rather than gained in the prophylactic cholecystectomy strategy.

The results of this decision analysis are limited for several reasons. First, the main outcome considered in the model was survival versus death. Possible risks (obstruction, pancreatitis and cholecystitis) and benefits (no morbidity from delaying surgery) were also considered. However, patient discomfort, symptoms and quality of life were not considered, nor were the disutility of tests, admission to hospital or emergency department visits in the wait-and-see group. Further, utilities for the various disease states were not considered, which the authors could have derived using standardized instruments.

Second, most of the probabilities were taken from a small number of relatively poor quality studies. It does not appear that the authors did a systematic review of the literature, so the chosen probabilities may not be representative. As well, the published rates vary widely, and it is not obvious why certain probabilities were chosen. For instance, several of the assumptions seem somewhat out of line with one of the author's own practice and would have the effect of favouring a prophylactic cholecystectomy. One such issue is the high rate (71%) of ERCP used in the gallstone pancreatitis population. There is a large literature on the cost-effectiveness of various strategies to assess potential choledocholithiasis in this patient population, and in most patients in whom the episode of pancreatitis was mild and settled quite quickly, less morbid approaches, such as operative cholangiography, are clearly a more appropriate option. Another factor is the long hospital stay reported: 8.6 days for patients with acute cholecystitis. For most patients with acute cholecystitis, a shorter length of stay can be achieved.

A third issue is the practice of

discharging patients after the pancreatitis has settled and bringing them back later for an outpatient cholecystectomy. These patients spent an average of 10 days in hospital for mild pancreatitis before they were discharged. Again, the experience of the authors is that these patients settle after an average of 3 to 5 days, and there is good evidence to show that definitive treatment before discharge is a more appropriate and cost-effective approach. Incorporating these practices into the model would almost certainly improve both the outcome and the economic analysis associated with the wait-and-see approach. The authors also assumed that the risk of death in a postcomplication cholecystectomy is the same as the risk of a prophylactic cholecystectomy, which is not necessarily true.

Another important point in interpreting the results relates to how large a life-years gain should be to be considered clinically important. The authors state that "during the 10-yr follow-up period, 23.2 life-years would be gained in the group of 5,000 patients." This gain is likely not clinically significant. However, the decision of whether to operate is more complex than the authors have expressed, because, most often, it is dependent on variables other than life-years, such as quality of life related to repeated episodes of biliary colic. This has not been quantified in the present model because no utilities were calculated.

Thus, this study is not likely to, and should not, change current practice. As the model showed, benefit is only seen when the risks of pancreatitis and mortality from gallstone pancreatitis are high. It is likely not appropriate to use such high values, because they represent extremes in the literature. It is also interesting that the authors report that 14%–17% of patients initially treated in the wait-and-see strategy would require cholecystectomy during the 10-year follow-up period—a figure that is almost identical to the number of

patients with asymptomatic gallstones who would require surgery in the Gracie and Ransohoff study. When the additional concerns identified in the preceding paragraphs are considered, it is clear that prophylactic cholecystectomy offers no advantage and likely offers a disadvantage to asymptomatic patients. However, the base case was a 45-year-old woman with a relatively short follow-up (10 yr), and the results might differ had they modelled patients of a different age group, patients with significant

comorbidities, or patients who were observed for a longer time. One finding that might have some clinical impact is the suggestion that determining gallstone size and number might affect the risk of future complications. If so, ultrasonographers might need to assess and report the number and size of stones when performing ultrasound examinations of the gallbladder and biliary tree. Although this study may be of limited value in assisting surgeons in deciding whether prophylactic cholecystec-

tomy should be performed, this area should continue to be of interest to clinicians, given the large population at risk. Identifying patients who might benefit from prophylactic intervention would be helpful.

Competing interests: None declared.

Reference

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