

# 1 Introduction

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Over the past three decades the emergence of evidence-based medicine (EBM) has had a substantial impact on clinical practice. In the first half of the twentieth century, diagnostic tests or treatments, usually based on a strong scientific rationale and experimental work in animals, were routinely introduced into clinical care without good scientific proof of efficacy in people. Some of these interventions, such as gastric freezing for the treatment of ulcers and penicillamine therapy for primary biliary cirrhosis, were ultimately shown to be ineffective<sup>1,2</sup> and harmful. There is little doubt that the widespread acceptance by physicians of unproved treatments has been detrimental to the well-being of many patients.

Fortunately, the need for a more critical approach to medical practice was recognized. In 1948 the first randomized controlled trial (RCT) in humans was carried out under the direction of the British Medical Research Council.<sup>3</sup> Epidemiologists and statisticians, notably Sir Richard Doll and Sir Bradford Hill, provided scientific leadership to the medical community, which responded with improvements in the quality of clinical research. The use of randomized allocation to control for confounding variables and to minimize bias was recognized as invaluable for conducting valid studies of treatments. The initiation of these landmark experiments defined a new era in clinical research; the RCT soon became the benchmark for the evaluation of medical and surgical interventions. Gastroenterologists played an important part in these early days. In 1955 Professor Sidney Truelove conducted the first randomized trial in the discipline of gastroenterology.<sup>4</sup> He and his colleagues proved that cortisone was more effective than a placebo for the treatment of ulcerative colitis. As noted in Chapter 11, this treatment has stood the test of time. The ascendancy of the RCT was accompanied by a call for greater scientific rigor in the usual practice of clinical medicine. Strong advocates of the application of epidemiological principles to patient care emerged and found a growing body of support among clinicians.

As the number of randomized trials grew to the point of becoming unmanageable, it was recognized that there was a need to provide summaries of the evidence provided by these trials for the use of practitioners, who frequently lack both time and expertise to consult the primary research. Busy

clinicians may consult local experts, with the tacit assumption that they will make recommendations based on evidence. Liberati and colleagues<sup>5</sup> provided evidence that this approach led to inappropriate care for many women with breast cancer. Subsequently, convincing evidence became available through the work of Antman *et al.*<sup>6</sup> and of Mulrow<sup>7</sup> that the conventional review article and the traditional textbook chapter are seldom comprehensive, and are frequently biased. More recently, Jefferson<sup>8</sup> reinforced this conclusion on the basis of a survey concerning recommendations for vaccination for cholera, which appeared in editorials and review articles. He pointed out that authors of editorials and reviews frequently resort to the “desk drawer” technique, pulling out evidence with which they are very familiar, but failing to assemble and review all of the evidence in a systematic way.

In the UK Archie Cochrane, as early as 1979, made a compelling case that there was a need to prepare and maintain summaries of all randomized trials.<sup>9</sup> Cochrane's challenge to the medical community to use scientific methods to identify, evaluate, and systematically summarize the world's medical literature pertaining to all health care interventions is now being met. From its inception in 1993, the electronic database prepared by the volunteer members of the Cochrane Collaboration and published as the *Cochrane Library*<sup>10</sup> has grown exponentially. Systematic reviews and especially Cochrane reviews are now widely used by clinicians in the daily practice of medicine, by researchers and by the public. Accordingly, data from systematic reviews published in the *Cochrane Library* are featured prominently in several chapters in *Evidence-based Gastroenterology and Hepatology*. Unfortunately, coverage in the *Cochrane Library* of topics in gastroenterology and hepatology is still far from complete.

Several other clinical epidemiologists played important roles in the evolution of evidence-based medicine. Beginning in the 1970s, David Sackett encouraged practicing physicians to become familiar with the basic principles of critical appraisal. Criteria developed by Sackett and others for the evaluation of clinical studies assessing therapy, causation, prognosis, and other clinical topics were widely published.<sup>11,12</sup> His text *Clinical epidemiology: a basic science for clinical medicine*, co-authored by colleagues Gordon

Guyatt, Brian Haynes and Peter Tugwell, introduced many physicians to the concepts of EBM.<sup>13</sup> In the USA, Alvin Feinstein called attention to the need for increased rigor in the design and interpretation of observational studies and explored the scientific principles of diagnostic testing.<sup>14,15</sup> Among gastroenterologists, Thomas Chalmers, a strong, early advocate for the RCT,<sup>16</sup> was responsible for introducing gastroenterologists and others to the importance of randomized trials in gastroenterology and hepatology<sup>17</sup> and to the concept of systematic reviews and meta-analysis as means of summarizing data from these studies.<sup>18</sup>

Despite the opposition of some,<sup>19</sup> the popularity of EBM continues to grow. Although the explanations for this phenomenon are complex, one factor is that many practitioners recognize that ethical patient care should be based on the best possible evidence. For this, and other reasons, the fundamental concept behind EBM – the use of the scientific method in the practice of clinical medicine – has been widely endorsed by medical opinion leaders, patients and governments.

### What is evidence-based gastroenterology and hepatology?

Evidence-based gastroenterology and hepatology is the application of the most valid scientific information to the care of patients with gastrointestinal and hepatic diseases. Physicians who treat patients with digestive diseases must provide their patients with the most appropriate diagnostic tests, the most accurate prognosis and the most effective and safe therapy. To meet this high standard individual clinicians must have access to and be able to evaluate scientific evidence. Although many practitioners argue that this has always been the standard of care in clinical medicine, a great deal of evidence exists to the contrary. Wide variations in practice patterns among physicians have been documented for many treatments, despite the presence of good data from widely publicized RCTs and the promotion of practice guidelines by content experts. For example, Scholefield *et al.* carried out a survey of British surgeons who were questioned regarding the performance of screening colonoscopy for colon cancer.<sup>20</sup> Although this study was done in 1998 (after publication of the results of the RCTs described in Chapter 16 which demonstrated a benefit of this practice), many of these physicians failed to make appropriate recommendations for screening patients at risk. What is the explanation for this finding? One possibility is that many clinicians rely for information on their colleagues, on local experts, or on review articles or textbook chapters that are not written based on the principles of EBM.

Two important points about EBM should be emphasized. First, use of the principles of EBM in the management of

patients is complementary to traditional clinical skills and will never supersede the recognized virtues of careful observation, sound judgment and compassion for the patient. It is noteworthy that many good doctors have intuitively used the basic principles of EBM; hence, the promotion of such well known clinical aphorisms as “go where the money is” and “do the last test first”. Knowledge of EBM enables physicians to understand why these basic rules of clinical medicine are valid through the use of a quantitative approach to decision making. This paradigm can in no way be considered detrimental to the doctor–patient relationship.

Second, although RCTs are the most valuable source of data for evaluating healthcare interventions, other kinds of evidence must frequently be used. In some instances, most obviously in studies of causation, it is neither possible nor ethical to conduct RCTs. Here, data from methodologically rigorous observational studies are extremely valuable. A dramatic example was the demonstration by several authors (quoted in Chapter 24) that the relative risk of hepatocellular carcinoma in chronic carriers of the hepatitis B virus is dramatically higher than in persons who are not infected. Although these data are observational, the strength of the association is such that it is exceedingly unlikely that a cause other than hepatitis B virus is responsible for the development of cancer in these people. Case–control studies are especially useful for studying rare diseases and for the initial development of scientific hypotheses regarding causation. The etiological role of non-steroidal anti-inflammatory drugs in the development of gastric ulcer<sup>21</sup> was recognized using this methodology. Finally, case series can provide compelling evidence for the adoption of a new therapy in the absence of data from RCTs, if the natural history of the disease is both well characterized and severe. An example is the identification of orthotopic liver transplantation as a dramatically effective intervention for patients with advanced liver disease.

Box 1.1 shows a generally agreed approach to ranking the strength of evidence that arises from various types of studies of healthcare interventions, and this system is used throughout the book. This ranking of evidence has appeared in a number of publications; we have chosen to reproduce it from *Evidence-based Cardiology*,<sup>22</sup> along with the system used by its editors, Yusuf *et al.*, for making recommendations on the basis of these levels of evidence. As mentioned in Box 1.1, throughout this book recommendation grades appear as **Grade A** or **Grade A1a**.

### Clinical decision making in gastroenterology and hepatology

Clinical decision making by gastroenterologists usually falls into one of the following categories:

**Box 1.1 Grading of recommendations and levels of evidence used in *Evidence-based Gastroenterology and Hepatology*****GRADE A**

- Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively have at least as much data as one single well-defined trial
- Evidence from at least one "All or None" high quality cohort study; in which ALL patients died/failed with conventional therapy and some survived/succeeded with the new therapy (for example, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and NONE died/failed with the new therapy (for example, penicillin for pneumococcal infections)
- Evidence from at least one moderate sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.
- Evidence from at least one RCT

**GRADE B**

- Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy
- Evidence from at least one high quality case control study
- Evidence from at least one high quality case series

**GRADE C**

- Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research or first principles)

A comprehensive approach would incorporate many different types of evidence (for example, RCTs, non-RCTs, epidemiologic studies and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally the evidence does not completely fit into neat compartments. For example, there may not be an RCT that demonstrates a reduction in mortality in individuals with stable angina with the use of  $\beta$ -blockers, but there is overwhelming evidence that mortality is reduced following myocardial infarction (MI). In such cases, some may recommend use of  $\beta$ -blockers in angina patients with the expectation that some extrapolation from post-MI trials is warranted. This could be expressed as Grade A/C. In other instances (for example, smoking cessation or a pacemaker for complete heart block), the non-randomized data are so overwhelmingly clear and biologically plausible that it would be reasonable to consider these interventions as Grade A.

Recommendation grades appear either within the text, for example, **Grade A** and **Grade A1a** or within a table in the chapter.

- Deciding whether to apply a specific diagnostic test in arriving at an explanation of a patient's problem, or determining the status of the patient's disease.
- Offering a prognosis to a patient.
- Deciding among a number of interventions available for managing a patient's problem. In this category, the first question is "Does a given intervention do more good than harm?" The second is "Does it do more good than other effective interventions?" The third is "Is it more or less cost effective than other interventions?"

**Application of a diagnostic test**

*Example* A 4-year-old child is experiencing diarrhea and has a positive family history of celiac disease. Should a serological test for antiendomysial antibody (EMA) be done?

Chapter 9 includes an extensive treatment of this topic with a summary of studies (see Table 9.1) that included various groups of patients with a greater or lesser probability of having celiac disease (ranging from patients with gastrointestinal symptoms to patients in whom celiac disease was suspected on clinical grounds). At least one of the studies in Table 9.1, that of Cataldo *et al.*,<sup>23</sup> is relevant to this patient.

When evaluating this test the reader may wish to adopt the approach of Kitching *et al.*<sup>24</sup> for deciding on the clinical usefulness of a diagnostic test (Figure 1.1).

The criteria listed in Figure 1.1 for validity of a diagnostic test were clearly met in Cataldo's study. In Chapter 9 Gregor and Alidina explores the utility of the test and points out that tests with high positive likelihood ratios ( $LR > 10$ ) and low negative likelihood ratios ( $LR < 0.1$ ) are generally considered to be clinically useful. The EMA test clearly falls into this category. The authors draws attention to the fact that the probability that a specific patient actually has celiac disease (based on a positive test), or does not have it (based on a negative test), also depends on the *pretest odds* of the patient having the disease (see Table 1.1).

If the child in question, whose pretest likelihood of celiac disease is estimated to be 8%, has a negative test it may be concluded that the child almost certainly does not have celiac disease; on the other hand, if the child has a positive test, the likelihood of him or her having celiac disease is still only 65%.

As Gregor and Alidina point out, the implications of misdiagnosis must be considered carefully. In the circumstance of a positive test in the child with non-specific symptoms the physician and the child's parents should consider whether it is now reasonable to proceed to intestinal

- **Are the study results valid?**

- 1 Was there an independent blind comparison (or unbiased comparison) with a reference ("gold") standard of diagnosis?
- 2 Was the diagnostic test evaluated in an appropriate spectrum of patients (like those seen in the reader's practice)?
- 3 Was the reference standard applied regardless of the diagnostic test result?

- **What are the results?**

Cataldo F, Ventura A, Lazzari R *et al.* Antiendomysium antibodies and celiac disease: solved and unsolved questions. An Italian multicentre study. *Acta Paediatr* 1995;**84**:1125–31.

A study of IgA endomysium antibodies (EMA) in 1485 children with gastrointestinal disease (688 with celiac disease confirmed by intestinal biopsy)

Results for antiendomysial antibody (EMA) test

	No. of patients with biopsy proven celiac disease		Totals
	Present	Absent	
EMA positive	645	20	665
	a	b	a+b
EMA negative	c	d	c+d
	43	777	810
	a+c	b+d	a+b+c+d
Totals	688	797	1485

Sensitivity =  $a/(a + c) = 645/688 = 0.94$

Specificity =  $d/(b + d) = 777/797 = 0.97$

Likelihood ratio (positive result) =  $\text{sensitivity}/(1 - \text{specificity}) = 0.94/(1 - 0.97) = 31$

Likelihood ratio (negative result) =  $(1 - \text{sensitivity})/\text{specificity} = (1 - 0.94)/0.97 = 0.06$

Positive predictive value =  $a/(a + b) = 645/665 = 0.97$

Negative predictive value =  $d/(c + d) = 777/810 = 0.96$

**Figure 1.1** Approaches to evaluating evidence about diagnosis

**Table 1.1** The anti-endomysial antibody (EMA) test for celiac disease. Dependence of post-test likelihood of celiac disease on pretest likelihood, assuming positive LR = 31, negative LR = 0.06

Pretest likelihood of celiac disease	Post-test likelihood with a positive EMA test (%)	Post-test likelihood with a negative EMA test (%)
8% (non-specific symptoms, positive family history)	65	0.5
50% (more specific symptoms)	97	6
0.25% (population screen)	8	0.02

Data from Chapter 9

biopsy to confirm the diagnosis, rather than recommending a gluten-free diet, presumably for life. If a search for other clinical or laboratory clues reveals that celiac disease is very likely to be the correct diagnosis, the pretest likelihood may be as high as 50%. This would raise the post-test likelihood to 97%. The physician and parents may be comfortable accepting the diagnosis and proceed to a trial of a gluten-free diet, rather than subjecting a young child to intestinal biopsy. This is an excellent example of how a skilled clinician must

integrate the principles of evidence-based medicine with traditional clinical skills and judgment.

### Offering a prognosis

*Example* A 50-year-old woman with recently diagnosed celiac disease has learned at a meeting of the local celiac society that patients with celiac disease have a substantial increase in the risk of developing a number of cancers and

**Table 1.2 Cancer mortality in 210 patients with celiac disease at the end of 1985**

Site of cancer	ICD8	O	E	O/E	P
All sites	140–208	31	15.48	2.0	**
Mouth and pharynx	141–147	3	0.31	9.7	*
Esophagus	150	3	0.24	12.3	*
Non-Hodgkin's lymphoma	200, 202	9	0.21	42.7	**
Gastrointestinal tract	151–154	3	3.07	1.0	NS
Remainder		13	11.65	1.1	NS

\* $P < 0.01$ .\*\* $P < 0.001$ .

O, observed numbers; E, expected numbers

Source: Holmes GKT *et al. Gut* 1989;**30**:333–8.<sup>25</sup>**Table 1.3 Cancer morbidity by diet group**

Site of cancer	Diet group <sup>a</sup>	No.	O	E	O/E	P
All sites	1	108	14	9.06	1.5	**
	2	102	17	6.42	2.6	
Mouth, pharynx, esophagus	1	108	1	0.33	3.0	**
	2	102	5	0.22	22.7	
Non-Hodgkin's lymphoma	1	108	2	0.12	16.7	*
	2	102	7	0.09	77.8	
Remainder	1	108	11	8.61	1.3	**
	2	102	5	6.11	0.8	

\* $P < 0.01$ .\*\* $P < 0.001$ .<sup>a</sup>Diet group 1, strict adherence to gluten-free diet; group 2, reduced gluten diet or normal diet.Source: Holmes GKT *et al. Gut* 1989;**30**:333–8.<sup>25</sup>

that this cancer risk is reduced by strict adherence to a gluten-free diet.

Chapter 9 describes the types of study which are relevant to determination of prognosis and discusses the strengths and weaknesses of case-control and cohort studies.

Gregor and Alidina point out that certain case-control studies which reported very high mortality and malignancy rates may have been subject to selection bias (inclusion of particularly ill or refractory patients) and measurement bias (patients with abdominal symptoms being more likely to undergo investigations such as small bowel biopsy which may lead to a diagnosis of celiac disease). They refer to a British study in which a cohort of patients with celiac disease was assembled and followed for 10 years. This design attempts to minimize the biases that are inherent in the case-control studies. Table 1.2 shows that the risk of certain cancers is increased compared to the risk in the general population. Table 1.3 shows that strict adherence to a gluten-free diet significantly reduced this risk and may have eliminated the excess risk for several of the identified cancers.

On the basis of this evidence it is reasonable to advise the patient that her disease does carry with it an increased risk of certain relatively uncommon cancers and that adherence to a strict gluten-free diet appears to minimize this increased risk.

### Recommendations concerning therapy

We have provided examples of how evidence concerning the use of diagnostic tests and prognosis can be analyzed and incorporated into clinical practice. Most chapters in this book deal more extensively with evidence concerning therapy and rely heavily on data from randomized trials and meta-analyses.

*Example* Should a 28-year-old woman who has had an uncomplicated resection of the terminal ileum for Crohn's disease receive maintenance therapy with a 5-aminosalicylate (ASA) product? Prior to the surgery she had had steroid-dependent disease and had failed treatment with both azathioprine and methotrexate.

• **Are the results valid?**  
 1 Was the assignment of patients to treatment really randomized (and the randomization code concealed)?  
 2 Were all patients who entered the study accounted for at its conclusion?  
 3 Were the clinical outcomes measured blindly?

• **Is the therapeutic effect important?**  
 1 Were both statistical and clinical significance considered?  
 2 Were all clinically important outcomes reported?

• **What are the results?**  
 McLeod RS, Wolff BG, Steinhart AH *et al.* Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995;**109**:404–13.

Randomized controlled trial in which 163 patients with Crohn's disease who had all visible disease resected were randomized to receive mesalamine (Pentasa) 3 g daily or a placebo for a median period of 34 months. Primary outcome was recurrent Crohn's disease defined by recurrence of symptoms and radiographic or endoscopic documentation of recurrence.

	Recurrent Crohn's disease		Risk (%)	ARR (%)	RRR (%)
	Yes	No			
5-ASA	27	60	31	10	24
Placebo	31	45	41	–	–

ARR, absolute risk reduction; RRR, relative risk reduction.

• **Are the results relevant to my patient?**  
 1 Were the study patients recognizably similar to my own?  
 2 Is the therapeutic maneuver feasible in my practice?

**Figure 1.2** Elements of a valid and useful randomized trial

A search of the literature for placebo-controlled randomized trials of 5-ASA for maintenance of remission in patients with a surgically induced remission of disease would reveal several trials. The largest published trial is that of McLeod and colleagues,<sup>26</sup> who randomized 163 adult patients to receive either 3 g/day of 5-ASA or a placebo following surgery. The primary outcome of interest was the recurrence of active Crohn's disease as defined by the recurrence of symptoms and the documentation of active disease either radiologically or endoscopically. At the end of the follow up period (maximum duration 72 months, median duration 34 months), 31% of patients who received active treatment remained in remission compared with 41% of those who received a placebo ( $P = 0.031$ ). 5-ASA was well tolerated. A low proportion of patients developed adverse reactions in the control and active treatment groups. One patient treated with 5-ASA developed pancreatitis that was attributed to the study drug. The results of this study can be evaluated using the guidelines described in Figure 1.2, which is modeled after the approach of Kitching *et al.*<sup>24</sup>

### Are the results of this study valid?

A review of the methods section of the article<sup>26</sup> confirms that an appropriate method of randomization was employed (computer-generated in permuted blocks), which insured concealment of the randomization code. Furthermore, inspection of the baseline characteristics of the treatment and control groups shows that they are well balanced with respect to such confounding variables as the time from surgery to randomization. This information further supports the legitimacy of the randomization process. Assessment of the method of randomization is important, because non-randomized designs are especially vulnerable to the effects of bias. Studies which employ "quasi-randomization" schemes such as allocation to treatment according to the day of the week or alphabetically by the patient's surname have been shown to consistently overestimate the treatment effect identified by RCTs that employ a valid randomization scheme.<sup>27,28</sup> However, it may be noted that 87 patients were randomized to 5-ASA, compared with only 76 patients in the control group. This observation raises the concern that the

analysis might not have been done according to the “intent to treat” principle which specifies that patients are analyzed in the group to which they were originally assigned, irrespective of the treatment that was ultimately received. The use of this strategy reduces the possibility of bias, which might occur if investigators selectively withdrew from the analysis patients who had done poorly or experienced toxicity. For this reason, the intent to treat principle yields a conservative estimate of the true benefit of the treatment. However, detailed review shows that in this study the discrepancy in patient numbers occurred because five patients who were randomized to the active treatment group withdrew consent prior to receiving the study medication and were not included. Thus it appears that the analysis was based on the intent to treat principle.

Approximately 10% of patients in both treatment groups had incomplete follow up. Methodologically rigorous studies have a very low proportion of patients for whom data are missing. This issue is important, since patients who are lost to follow up usually have a different prognosis than those for whom complete information is available. If there is incomplete follow up data for a substantial proportion of patients the results are uninterpretable.<sup>29</sup>

Turning to an assessment of the outcomes in this study, both the patients and investigators were unaware of the treatment allocation. Blinding is used to reduce bias in the interpretation of outcomes. This is especially important when a subjective outcome is evaluated.<sup>30</sup> In this study objective demonstration of recurrent disease (endoscopy and/or radiology) was required in addition to the more subjective measure of the introduction of treatment for recurrent symptoms. Thus the reader can be satisfied that the primary outcome measure was both clinically meaningful and objectively assessed.

Finally, the data analysis and results should be examined. A great deal of useful information can be obtained by reviewing the assumptions that were used in the sample size calculation. In this study, which analyzes a difference in proportions, the investigators had to define four variables: the alpha (type 1) error rate, the beta (type 2) error rate, the expected proportion of patients who would be expected to relapse in the placebo group, and the minimum difference in the rate of relapse which the investigator wished to detect. In this publication these parameters are easily identified. The rate of symptomatic recurrence was estimated to be 12.5% per year and it was anticipated that treatment with 5-ASA would reduce this rate by 50% to an absolute value of 6.25% per year. In contrast to the expected 50% relative risk reduction which was anticipated, the 3-year *actuarial* risk of recurrence was 26% in the treatment group compared to 45% in the group that received 5-ASA ( $P=0.039$ ). Therefore, the relative risk reduction ( $[(45\% - 26\%) / 45\% = 42\%]$ ) is slightly lower than the figure which the investigators considered to be clinically meaningful. Furthermore, the probability of a type 1

error is described as a one-tailed value of  $P=0.05$ . This implies that one-tailed statistical testing was used to derive the  $P$  value of 0.039. The use of one-sided statistical testing raises legitimate concerns regarding the statistical inferences made in the study.<sup>31</sup> It is inappropriate to hypothesize that 5-ASA therapy could *only* be beneficial, given that the drug can cause diarrhea and colitis.<sup>32</sup> For these reasons, uncertainty exists regarding both the clinical and statistical interpretation of these data.

### Are the results of this valid study important?

To assess the importance of this result it is necessary to quantify the magnitude of the treatment effect. How the evidence is presented may influence both physicians and patients in making choices. The most basic means of expressing the magnitude of a treatment of fact is the absolute risk reduction (ARR), which is defined as the proportion of patients in the experimental group with a treatment success minus the proportion of patients with this outcome in the control group. In this instance the annual rate of relapse in the placebo-treated patients was 15% (success rate of 85%) compared with 8.7% (success rate of 91.3%) in those who received the active treatment. This yields an ARR of 6.3%. The number needed to treat (NNT), the number of patients with Crohn's disease who would have to be treated with 3 g/day of 5-ASA to maintain remission over a year, can be calculated as the reciprocal of this number, and is 16. Alternative ways of describing effectiveness include calculating the observed relative risk reduction ( $RRR = 6.3/15$ ) of 42%, or even stating that about 90% of patients respond to maintenance therapy, ignoring the substantial placebo effect which is evident. The evidence presented as the ARR or NNT, rather than the numbers which show the treatment in a more favorable light, may still lead the physician to recommend this form of treatment and cause the patient to choose to accept this strategy over no intervention. However, the expectations of the physician and patients are likely to be more realistic<sup>33</sup> than they may be if the physician accepts and promotes in an uncritical way the information that 90% of patients who receive 5-ASA maintenance therapy will remain in remission over 1 year.

### Are these results applicable to my patient?

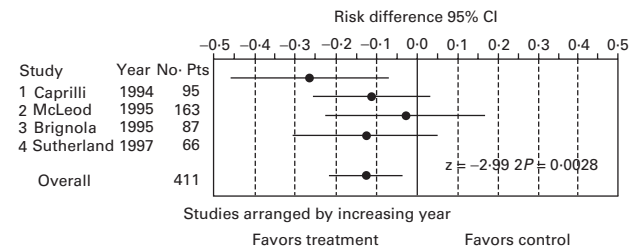
Following an assessment of the validity of the evidence using the criteria described in the preceding paragraphs it is necessary to decide whether the conclusions of the study are relevant and important to the individual patient. An initial step is to evaluate the demographic characteristics of the patients in the RCT and compare them to those of the patient

in question. If the patient for whom maintenance therapy is being considered is similar to the patients who were evaluated in the trial, it is reasonable to assume that she will experience the same benefit of therapy and is at no greater risk for the development of adverse drug reactions. Alternatively, this patient may have characteristics that make it unlikely that a benefit from 5-ASA will be realized. For example, if the patient had residual active Crohn's disease it would be difficult to generalize the results of the study of McLeod *et al.*,<sup>26</sup> since the patients in this trial had resection of all visible disease prior to study entry.

At this point, if we accept that the results are generalizable to our patient example, the relative risks and benefits of the therapy must be weighed and the patient's preferences should be considered. Evaluation of the data reveals that the trial was methodologically rigorous and evaluated an important outcome. However, it is doubtful whether conventional statistical significance was demonstrated. This raises the question of whether the observed differences between the treatment groups might have occurred by chance. Furthermore, the magnitude of the treatment effect is relatively small. In presenting to the patient the benefit of an annual reduction in the risk of recurrence of 6.3% it is also necessary to consider the cost and inconvenience of taking medication for an asymptomatic condition. One observation in favor of recommending the treatment is that the risk of serious toxicity with 5-ASA appears to be low.

Because there is a degree of uncertainty concerning the true benefit of 5-ASA maintenance therapy based on analysis of this single RCT, it would be prudent to review additional published data. A meta-analysis of 5-ASA therapy has been published.<sup>34</sup> Meta-analysis, the process of combining the results of multiple RCTs using quantitative methods, is an important tool for the practitioner of EBM. Pooling the results of multiple RCTs increases statistical power and thus may resolve the contradictory results of individual studies. Combining data from RCTs statistically also increases the precision of the estimate of a treatment effect. Moreover, the greater statistical power afforded by meta-analysis may allow insight into the benefits of treatment for specific subgroups of patients. These properties are particularly relevant to the case under consideration, given the previously identified concerns.

The meta-analysis summarized data from 15 RCTs which evaluated the efficacy of 5-ASA maintenance therapy in 1371 patients with quiescent Crohn's disease. Patients were randomly assigned to receive either 5-ASA or placebo for treatment periods of 4–48 months. Although 5-ASA was superior to placebo in 13 of the 15 studies, the results of only two trials were statistically significant. Separate analyses were done using data from the four trials that included patients with a surgically induced remission (Figure 1.3) in distinction to those that evaluated patients after a medically induced remission. Sensitivity analyses assessed the response to



**Figure 1.3** Meta-analysis of the four RCTs of mesalamine for prevention of clinical relapse in quiescent Crohn's disease after surgically induced remission. Cumulative risk difference and the respective 95% CIs are shown. (Reproduced with permission from Camma C *et al. Gastroenterology* 1997;**113**:1469<sup>34</sup>)

therapy in specific subgroups of patients. The overall analysis concluded that 5-ASA has a statistically significant benefit; the risk of symptomatic relapse in patients who received 5-ASA was reduced by 6.3% (95% confidence interval -10.4% to -2.1%,  $2P=0.0028$ ), which corresponds to an NNT of 16. Importantly, the greatest benefit was observed in the four trials that evaluated patients following a surgical resection. In these studies there was a 13.1% reduction in the risk of a relapse (95% CI -21.8% to -4.5%,  $2P=0.0028$ ), which corresponds to an NNT of 8. No statistically significant effect was demonstrable in the analysis, which was restricted to the patients with medically induced remission.

### Are the results of this meta-analysis valid and reliable?

Figure 1.4 provides some useful guidelines for the interpretation of overview analyses. It is important that a comprehensive search strategy be adopted since publication bias, the selective publication of studies with positive results, is an important threat to the validity of meta-analysis.<sup>35</sup> This criterion was met. Camma and colleagues' review of the literature was extensive and not limited to English language publications. The investigators also searched review articles, primary studies and abstracts by hand. Quality scores were used to evaluate the validity of the individual studies and a sensitivity analysis was done which assessed the effect of trial quality on the result. No important change in the overall result was noted when studies of lower quality were excluded from consideration. However this type of analysis was not carried out in the analysis of the subgroups of four trials (411 patients) which evaluated 5-ASA after a surgically induced remission.

One of the included studies, that of Caprilli *et al.*,<sup>36</sup> which involved 95 patients, showed a greater benefit for 5-ASA than

- Are the results of this overview valid and reliable?
  - 1 Is it an overview of randomized trials of treatments?
  - 2 Does it include a methods section that describes:
    - (a) finding and including all the relevant trials?
    - (b) assessing their individual validity?
    - (c) using valid statistical methods that compare "like with like" stratified by study?
  - 3 Were the results consistent from study to study?
  - 4 Are the conclusions based on sufficiently large amounts of data to exclude a spurious difference (type 1 error) or missing a real difference (type II error).
- Are these applicable to your patient?
 

Differences between subgroups should only be believed if you can say "yes" to all of the following:

  - 1 Was it hypothesized before the study began (rather than the product of dredging the data), and has it been confirmed in other, independent studies?
  - 2 Was it one of just a few subgroups analyses carried out in this study?
  - 3 Is the difference both clinically (beneficial for some but useless or harmful for others) and statistically significant?
  - 4 Does it really make biologic and clinical sense?

**Figure 1.4** Approaches to evaluating evidence concerning overviews. (Reproduced from Yusuf S *et al.*, eds. *Evidence-based Cardiology*. London: BMJ Books, 1998<sup>22</sup>)

any other trial, medical or surgical, which has been performed. An important methodological deficiency of this RCT was the failure to conceal the treatment allocation from the investigators. Since these physicians were aware of the treatment assignment, and the definition of relapse used required clinical interpretation, it is possible that the 27% reduction in the risk of relapse identified is an overestimation of the true treatment effect. Accordingly, the inclusion of the results of this study in the subgroup analysis of the surgical studies may overestimate the true benefit of 5-ASA. Furthermore, Camma *et al.* did not include an additional trial by Lochs<sup>37</sup> which was only available as a preliminary report at the time the meta-analysis was done. This study, which is the largest RCT to evaluate 5-ASA following surgery, assigned 318 patients to receive either 4 g of active drug or a placebo for 18 months. Although Camma and colleagues described this study as "confirming" a benefit of 5-ASA after surgery, the results are not impressive. Only a 6.9% reduction in the rate of relapse was observed in patients who received the active treatment (24.5% 5-ASA compared with 31.4% placebo). This difference was *not* statistically significant.

This example underscores the importance of updating systematic reviews as new information becomes available, which is the approach of the Cochrane Collaboration, but not of reviews in conventional publications. When the data provided by Lochs *et al.* were aggregated with those of the other trials, the overall estimate of benefit for 5-ASA was less (ARR 4%, NNT 25).<sup>38</sup> On the basis of these data it can be concluded that 5-ASA may be an effective maintenance therapy following surgery, but if it is the magnitude of the treatment effect is modest at best.

### Are these results applicable to our patient example?

The meta-analysis of surgical trials by Camma *et al.* provides important information to the clinician who must decide whether or not to offer patients 5-ASA for maintenance therapy. The concern regarding statistical significance raised by the critique of the McLeod study has been reduced. It seems likely that the beneficial effect of 5-ASA following surgery is real. However, although the majority of the criteria outlined in Figure 1.4 have been met, the issue of clinical relevance remains. The most optimistic estimate of the size of the treatment effect, derived from the meta-analysis, is an NNT of 8. However, given the possibility of bias in the study of Caprilli *et al.*, a more conservative estimate could be based on the data of Lochs and colleagues from the single large randomized trial which yielded an NNT of 15 or from the revision by Sutherland of Camma's meta-analysis that yielded an ARR of only 4%, and an NNT of 25.

In presenting this information to the patient the following points should be emphasized.

- The existing data suggest that 5-ASA is not effective, or at the most, very marginally effective.
- The annual risk of relapse following surgery is relatively low without treatment.
- 5-ASA therapy is safe.
- The cost of 5-ASA therapy is approximately US\$70 per month.
- To derive a benefit from the treatment the medication must be taken on a regular basis. This requires the patient to take six pills each day.

Patients undoubtedly will react in different ways to this information. Our patient chose not to accept this therapy.

### Rationale for a book on evidence-based gastroenterology and hepatology

Gastroenterologists, hepatologists and general surgeons are fortunate to have many excellent textbooks that provide a wealth of information regarding digestive diseases. Such traditional textbooks concentrate on the pathophysiology of disease and are comprehensive in their scope. *Evidence-based Gastroenterology and Hepatology* is not intended to replace these texts, since its focus is on clinical evidence.

Excellent electronic databases are available, and many traditional publications contain relevant research evidence and important summaries and reviews to support evidence-based practice. However, Cumbers and Donald<sup>39</sup> have found that physicians in clinical practice find the acquisition of data from these sources time consuming. Their study revealed that even locating relevant articles required on average 3 days for practitioners with an onsite library and a week for those without such a facility. This book has been written for the purpose of saving valuable time for busy practitioners of gastroenterology and hepatology, and for general internists and general surgeons who deal with substantial numbers of patients with disorders ranging from gastroesophageal reflux disease to liver transplantation. It has been extensively revised since the first edition was published in 1999 in order to provide more recent evidence that serve as the basis for recommendations. For example strong evidence that infliximab is beneficial in Crohn's disease is presented in this edition along with a careful consideration of its adverse effect profile.

The book cannot claim to be comprehensive; for example, the reader will not find chapters on the management of traveler's diarrhea, infectious enterocolidities or acute diverticulitis. However, since the first edition of this book was published, chapters have been added on antibiotic-associated diarrhea, microscopic and collagenous colitis, esophageal motility disorder, management of Barrett's metaplasia of the esophagus, Ogilvie's syndrome, management of obesity, management of hepatitis B and C after liver transplantation and non-alcoholic steatohepatitis. These chapters have been added to provide the reader with more complete coverage of topics. Nevertheless, in arriving at the composition of the book for the second edition, we have had to establish a list of priority areas where we felt that there was important evidence to be reviewed and summarized on one hand and available authors with the required expertise on the other. We hope that future editions will expand further the number of topics that are included.

A limitation of any textbook is the timeliness of the information that it is possible to provide in print form. New

evidence accumulates rapidly in clinical medicine and it is impossible to include the most up-to-date information in a textbook because of the time required for production. To meet the needs of our readers for the most timely information the editors have endeavored to include, where possible, new evidence that became available during the editorial process. It is also planned to produce electronic updates of chapters at regular intervals. These updates, like those for the companion book *Evidence-based Cardiology*, will appear on the BMJ website ([www.bmj.com](http://www.bmj.com)).

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