CHAPTER 1
Evidence-based practice

1.1 Why evidence-based practice?

We all like to think we are practicing medicine based on the best evidence available. However, we sometimes do things in medicine for one or more of the following reasons:

- "It has always been done that way"
- "Everyone does it that way"
- "The consultant says so"
- "The protocol says so"

We tend not to challenge the dogma because we are too busy or because we do not know how to find the evidence or because we think we know the evidence. If doctors are asked what are the main obstacles to them in trying to review the literature, the commonest answers are lack of time,[1–5] followed by lack of knowledge.[4,5] However, innovations have made it much easier and quicker to search the literature.

Sometimes the best evidence available for a clinical decision will be a high-quality systematic review of several good RCTs on patients like yours (see Section 1.5, p. 2). At other times, there may be no trials and the only evidence will be from observational studies, such as case series or even case reports. A clinician making the clinical decision will find it helpful to know the strength of the evidence and the degree of uncertainty in making that decision.

Young doctors should be encouraged to challenge dogma and to ask for the evidence supporting management whenever possible. Senior doctors should be quick to ask the young doctors to look it up themselves and return with the evidence. We should all be open-minded enough to accept that our current practices may be wrong and not supported by the evidence.

In the past our attempts to practice in an evidence-based way were hampered by difficulty in getting easy access to the evidence. Literature searches were cumbersome and evidence was rarely presented to us in a convenient or easily digestible way. That is no longer an excuse. Anyone with Internet access has immediate access to the best evidence and can review the recent literature in a few minutes.

The concept of evidence-based medicine (EBM) was developed by Sackett and colleagues at McMaster University in Canada during the 1980s and 1990s. They defined EBM as the integration of the best research evidence with clinical expertise and patient values.[6] Our ability to practice EBM has been enhanced by the development of systematic ways of reviewing the literature and the availability of search engines to find the evidence.

1.2 The Cochrane Library

The Cochrane Collaboration has revolutionized the way we look at evidence. The Cochrane Collaboration was founded in 1993 and named for the British epidemiologist Archie Cochrane. It is an international non-profit-making organization that produces systematic reviews (see Section 1.5, p. 2) of health-care interventions and makes sure they are updated regularly. We consider that a good Cochrane systematic review provides the best available evidence on interventions. This is because a Cochrane review involves a formalized process of finding all published and unpublished studies, assessing their quality, selecting only those studies that meet predetermined criteria, and performing a meta-analysis when possible. A meta-analysis is a way of combining the results from several studies to get an overall mathematical summary of the data.

Cochrane reviews are only about interventions, which often but not always involve treatment. Cochrane reviews on treatment usually include only RCTs because an RCT is the best study design for avoiding bias when assessing treatment. When considering the evidence for any intervention, it is almost always worth

searching the Cochrane Library before looking elsewhere.

A Cochrane review takes on average 700 hours of work, so we are privileged to have ready access to such information, presented clearly in the Cochrane Library. Even if the Cochrane reviewers find no RCTs or only one, the knowledge that there is only scanty evidence on which to base clinical decisions is itself valuable.

The Cochrane Library is free in developing countries and in the UK, where the National Health Service (NHS) pays for it. It requires a subscription in the USA and Australia, but many libraries and hospitals subscribe. Abstracts of Cochrane reviews are available free to all through PubMed. The Web site for the Cochrane Library is http://www.thecochranelibrary.com/.

1.3 Clinical evidence

Another extremely useful resource is Clinical Evidence, which is a collection of systematic reviews from the BMJ. Clinical evidence is free in developing countries and in the UK, where the NHS pays for it. It requires a subscription in the USA, but many libraries subscribe, and it is currently distributed free to US primary care physicians through an American foundation. The Web site is http://www.clinicalevidence.com/.

1.4 Medline and PubMed

PubMed is a means of easy access to Medline, the comprehensive database provided free to all users by the US National Library of Medicine and the National Institutes of Health. It allows access to the abstracts of thousands of publications from many scientific journals. In addition, if when looking at the abstract the journal logo appears on the right side of the screen, clicking the logo often allows free access to the whole paper. The Web site is http://www.pubmed.gov/.

1.5 Hierarchy of evidence

For studies relating to treatment, which will be the most frequent scenario in this book, there is an accepted hierarchy of evidence, based on study design. This is because any studies where patients are not randomly allocated to one or other treatment (randomized) are likely to be affected by bias. This is not to say there is intentional bias. However, in a non-randomized study, the groups may differ significantly. One group may be more severely affected than the other. An example is preadmission antibiotics for suspected meningococcal infection. A cohort study compared the outcome in a non-randomized group of patients with suspected meningococcal infection given preadmission antibiotics to the outcome in patients not given antibiotics.[7] Patients given antibiotics were more likely to die than patients not given antibiotics. It might appear that antibiotics increase mortality, but the patients given antibiotics are likely to have been sicker than those not given antibiotics. Thus there was bias and the groups were not truly comparable. Studies that do not involve randomized patients are sometimes called "observational studies."

In general, a Cochrane review (see Section 1.2, p. 1) will give better evidence than a non-Cochrane systematic review and so on, although it is important for you to assess the quality of any evidence, including that from Cochrane and non-Cochrane systematic reviews. Weak data can lead to misleading conclusions.

1 *Cochrane review:* A peer-reviewed systematic review, usually of RCTs, using explicit methods and published in the Cochrane Library's Database of Systematic Reviews.

[A Cochrane review is only as good as the quality of the studies included. In many reviews, a meta-analysis is possible, summarizing the evidence from a number of trials.]

2 *Systematic review (non-Cochrane):* A review that systematically searches for all primary studies on a question, appraises, and summarizes them. Systematic reviews that evaluate treatment usually include RCTs rather than other study types.

[The abstracts of non-Cochrane systematic reviews can be found in PubMed under "Clinical Queries," and the abstracts of good-quality systematic reviews are in the Cochrane Library's Database of Abstracts of Reviews of Effectiveness.]

3 *Meta-analysis:* A meta-analysis is a mathematical summary in which the results of all the relevant studies are added together and analyzed, almost as if it had been one huge trial.

4 *RCT:* Subjects are randomly allocated to an experimental (treatment) group or a control (placebo or different treatment) group and the outcome studied.

5 *Cohort study:* A non-randomized study of two groups of patients. One group receives the exposure of

interest (e.g., a treatment) and the other does not. The study on preadmission antibiotics for meningococcal infection[7] is an example.

6 *Case-control study:* Patients with the outcome being studied are matched with one or more controls without the outcome of interest and compared regarding different exposures to look for risk factors for or predictors of the outcome. For example, a group of children with a rare outcome, say tuberculous meningitis (TBM), could be compared with matched controls without TBM with regard to BCG vaccination, contact with TB, socioeconomic factors, etc., to determine factors that appear to protect against TBM (such as BCG) and risk factors (such as contact with TB and possibly socioeconomic status).

7 *Case series:* Reports of a series of patients with a condition but no controls.

8 *Case reports:* Reports of one or more patients with a condition.

The hierarchy of evidence of studies does not apply to evidence about etiology, diagnosis, and prognosis:

The best evidence about **etiology** is from large cohort studies or case-control studies or sometimes RCTs.

The best evidence about **diagnosis** is from large cross-sectional studies in a similar population to yours, because the results will be most relevant to your clinical practice. In these studies, the test or tests you are interested in is compared to a reference test or "gold standard." For example, a new test like polymerase chain reaction for respiratory syncytial virus might be compared to viral culture.

The best evidence about **prognosis** is from large cohort studies, in a population like yours, followed over time. The no-treatment or placebo groups from large RCTs can provide excellent data on prognosis also.

The hierarchy of evidence is an oversimplification. It is also important to decide how the results apply to your patients. In general, you need to think whether there are biological reasons why the treatment effect could differ in your patients. Often there are more data for adults than children, as in the Cochrane systematic review of sore throat[8] we discuss later. Should you ignore data from adult studies or are these relevant? For example, is the biology of appendicitis so different in adults compared with children that you can learn no relevant information from studies done entirely in adults?

The other question you always need to consider is "What is the baseline risk in my population?" in order to work out how much your particular patient will benefit. For example, how likely is my patient to have prolonged symptoms from acute otitis media, and by how much would this be reduced by applying the relative risk for antibiotic treatment (measured as a relative risk or odds ratio)?

1.6 Searching the literature

The busy clinician will save time by looking for sources of summarized evidence first. If you have access to the Internet, the easiest initial approach is to look first in the Cochrane Library if available (for systematic reviews and RCTs), then in Clinical Evidence if available, and then in Medline via PubMed. If the programs are not already available on your computer, you can find them by going straight to the Web sites http://www.thecochranelibrary.com for the Cochrane Library, http://www.clinicalevidence.com/ for Clinical Evidence, and http://www.pubmed.gov/ for PubMed. The Web addresses can then be saved as favorites.

Framing the question

The next step is to decide on search terms. It will be a lot easier to search the literature if you can frame the question well.[9] Most questions about treatment in this book are framed in the classic evidence-based PICO format,[9] where P = Population, I = Intervention, C = Comparison, and O = Outcome. Suppose you are interested in whether or not antibiotics are indicated for sore throat in children (see Figure 1.1). Framing the question in the PICO format, you ask "For children with sore throats (Population), do antibiotics (Intervention) compared to no antibiotics or placebo (Comparison) reduce the duration of illness or reduce the frequency of complications (Outcome)?"

Searching for a Cochrane systematic review

You type the search terms "tonsillitis child" or "sore throat" or "sore throat child" into the Cochrane Library search window (where it says "Enter search term" in Figure 1.2) and find that there is a Cochrane systematic review by Del Mar et al.[8] The Cochrane reviewers

Frame the question:	Population	Intervention	Comparison	Outcome
	Children with sore throat or tonsillitis	Antibiotics	No antibiotics or placebo	Duration of illness or frequency of complications
Search the literature:	Cochrane Library: find a Cochrane review of antibiotics for sore throat in adults and children			
Assess the evidence:	Results: • Six patients need to be treated with antibiotics to cure one extra sore throat at day 3 • Antibiotics reduce the frequency of complications • Antibiotics more effective when patient has group A streptococcal infection • Difficult to distinguish between adults and children in the studies, and no subgroup analysis of children was possible • The evidence is most relevant for children 3 years and older, because the benefits of antibiotics will be less for younger children, who are much more likely to have viral infection causing their sore throat			
Decide on action:	Decide if your patient is similar to those studied. If your patient is more likely to have group A streptococcal infection, the benefits of starting antibiotics immediately are likely to be greater			

Figure 1.1 Answering a clinical question about treatment.

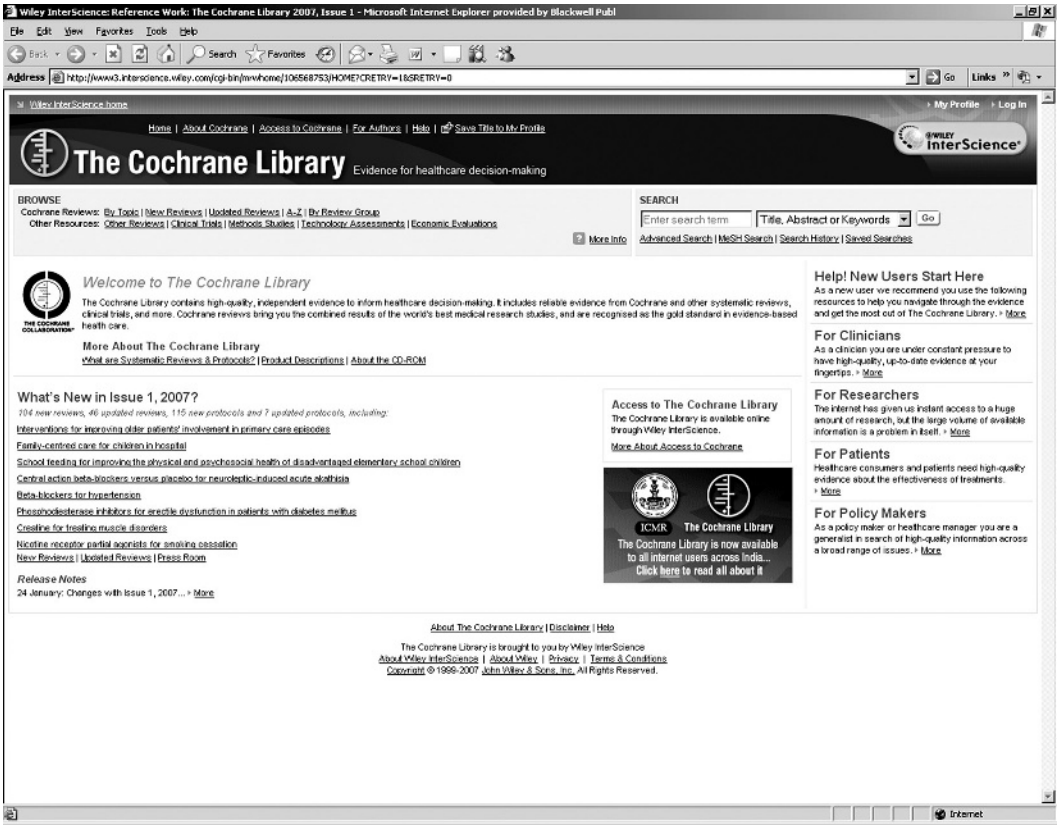

Figure 1.2 The Cochrane Library home page.

include 27 RCTs, perform a meta-analysis, and present conclusions about the benefits and risks of treating sore throats with antibiotics based on current evidence.[8] When you assess the relevance of the Cochrane review to your patient(s), you note that very few of the studies were performed only in children and the studies that include adults and children do not separate them out clearly. This is a common problem when searching the literature for evidence about children. You search the evidence further for variations in etiology and find that case series show a low incidence of group A streptococcal infection and a high incidence of viral infection in children younger than 3 years with tonsillitis. You make a clinical decision for your patient(s) based on your assessment of the literature (see also p. 176).

Searching for a non-Cochrane systematic review

If you do not find a Cochrane systematic review, you may find a systematic review in Clinical Evidence. If neither is successful, you may still find a quick answer to your clinical question. For example, you see a patient with hepatitis A. The books tell you to give normal human immunoglobulin to household contacts, but you wonder about the strength of the evidence. When you enter "hepatitis A" into the Cochrane Library search, you get 53 "hits," but most are about hepatitis B and hepatitis C. You find a Cochrane systematic review on vaccines for hepatitis A, and a protocol for immunoglobulin and hepatitis A but no data. There is nothing in Clinical Evidence on hepatitis A.

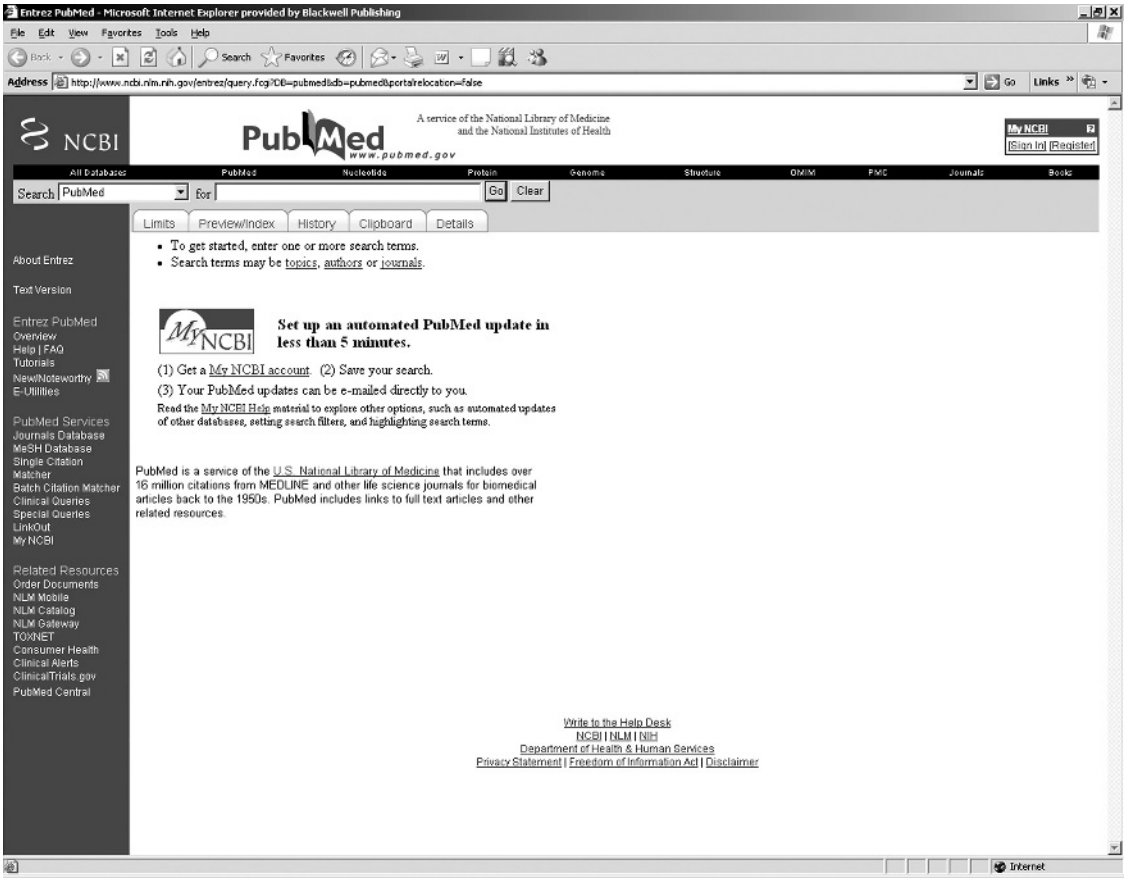

Figure 1.3 PubMed home page.

You turn to Medline using PubMed to look for a systematic review first. The best way to search rapidly for these is to use the "Clinical Queries" option. When you click "Clinical Queries," under PubMed services on the left-hand side of the PubMed home page (Figure 1.3), a new screen appears (Figure 1.4). There is an option "Find systematic reviews." When you enter "hepatitis A" into the box and click "Enter," you get 77 hits. But if you enter "hepatitis A immunoglobulin," you get 15 hits, of which the third is a systematic review of the effectiveness of immune globulins in preventing infectious hepatitis and hepatitis A. The systematic review says post-exposure immunoglobulin was 69% effective in preventing hepatitis A infection (RR 0.31, 95% CI 0.20–0.47).[10]

Searching for a meta-analysis

Suppose your search does not reveal a systematic review. For example, you want to know if immunoglobulin can prevent measles. You find no systematic reviews in the Cochrane Library, Clinical Evidence, or PubMed. Your next question is whether there is a meta-analysis. You can look for a meta-analysis in PubMed using the "Limits" option, at the top left hand of the home page screen (Figure 1.3). You enter the search term "measles," click "Limits," and a number of options appear. Down the bottom of the page on the left is the heading "Type of Article." You click "Meta-Analysis," then click "Go," and find there are 16 meta-analyses of measles listed, mostly about immunization and vitamin A, but none is relevant to your question.

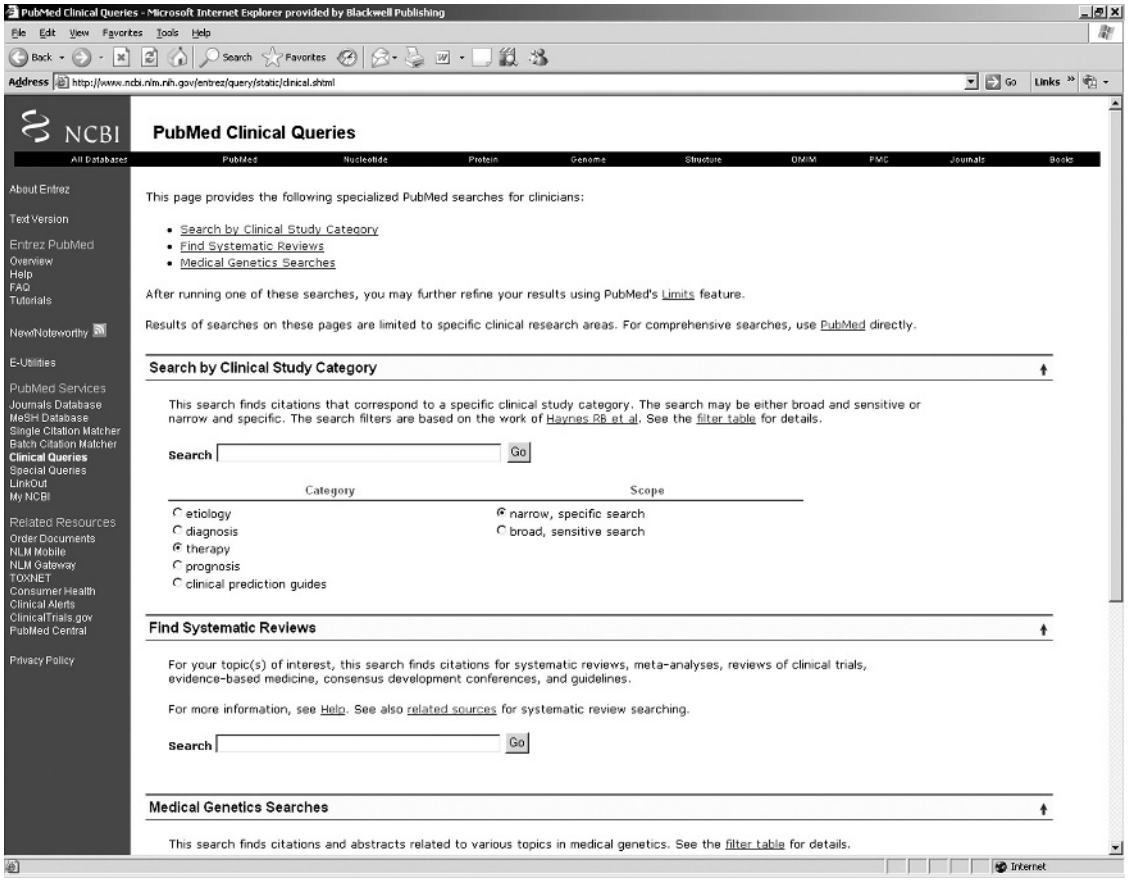

Figure 1.4 PubMed "Clinical Queries" page.

Searching for RCTs

If there is no systematic review and no meta-analysis, are there any RCTs? The best way to search rapidly for these is to use the "Clinical Queries" option again, but this time use the "Search by Clinical Study Category" option (the top box on Figure 1.4). You note this is already set on "therapy" and a "narrow, specific search," because these settings automatically find all RCTs, the commonest type of clinical query. When you put in your search term "measles and (immunoglobulin or immune globulin)" and click "Go," the program comes up with 94 RCTs. Most of the studies are irrelevant and can be ignored (this always tends to be the case). When you scan the titles and the abstracts, only one is helpful, and this shows that post-exposure prophylaxis with immunoglobulin could not be shown to be effective, reducing the risk of infection by only 8% with wide confidence intervals (less than 0–59%) that crossed zero, so the result is not statistically significant.[11] The study does not tell you whether immunoglobulin reduced severity. You conclude that there is no good evidence that giving post-exposure immunoglobulin prevents measles, and you can find no RCT data to say whether or not it reduces severity.

If you find no RCTs, you may need to try different search terms to make sure that it is not because you are asking the wrong question. There is a lot of trial and error in searching the literature and you will improve with practice.

Searching for non-randomized studies

If you use "Clinical Queries" but change from a "narrow, specific search" to a "broad, sensitive search," this gives you all clinical trials on the topic, not just RCTs.

Searching for questions about diagnosis

You can also use PubMed to search for questions about diagnosis, such as the best tests available to diagnose a condition. It is best to use "Clinical Queries" again, but this time when you get to the "Clinical Queries" page (Figure 1.4) select "diagnosis" before or after entering your search terms. This automatically takes you

Table 1.1 Relationship between question type, study type, and best source of evidence.

Question Type	Information Sought	Study Type	Best Source of Evidence
Treatment	Comparison of current best practice with a new therapy or comparison of new therapy with placebo	Systematic reviews of RCTs (with or without meta-analysis); RCTs; clinical practice guidelines (if based on a systematic review of the literature and an assessment of the quality of the evidence)	Cochrane Library Clinical Evidence Clinical practice guidelines Medline (PubMed) Evidence-based Web sites
Baseline risk (frequency)	Disease incidence; or disease prevalence; or frequency of complications	Population-based studies or cohort studies	Medline (PubMed) Review articles Textbooks
Etiology	Cause of disease	Cohort studies; case-control studies; RCTs when the question is about an adverse effect of an intervention	Cochrane Library Clinical Evidence Medline (PubMed)
Diagnosis	Information about the accuracy of a test, its capacity to identify a specific disorder and to distinguish the disorder from other disorders, and the applicability of a test to a particular patient population	The best studies allow an independent blind comparison between the test and the reference ("gold") standard for diagnosis	Cochrane Library Medline (PubMed)
Prognosis	Outcomes of disease: short and long term	Cohort studies or no treatment/placebo arm of RCTs	Medline (PubMed) Textbooks

to studies that give specificity (if you stay on "narrow, specific search") or sensitivity and specificity (if you select "broad, sensitive search").

Table 1.1 gives a guide to the most likely places to find the evidence you are seeking depending on the type of question. For a more comprehensive description of EBM and its application to clinical practice, we refer you to recent comprehensive but readable books.[9,12]

The sort of quick search described above should take you 10–15 minutes. You will improve with practice. If you are scared of trying, you will never know how easy and satisfying it is to scan the literature and find quite good evidence you never knew existed.

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