

# HOW TO USE EVIDENCE BASED MEDICINE IN EVERYDAY CLINICAL PRACTICE

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## Introduction

Evidence Based Medicine (EBM) is a young discipline involved with the systematic review of published studies to provide the best evidence to answer a clinical question. It is not a technique for insurers to limit payments or access, but has been used in that fashion. It is not a proscriptive way of practicing the art of medicine, but a tool to find quickly find and to use, new information. Because a lot of what we know is wrong. In medical school, my professors knew that mammalian neural cells did not reproduce in mature animals. Now we know differently and stem cell research holds enormous promise in treatment of neurological disease. EBM also developed as a method to rapidly educate or reeducate clinicians on advances in their field. David Sackett and his colleagues at the Centre for Evidence Based Medicine at Oxford, have been in the forefront of this emerging field.

At the center of EBM is the formation of a focused clinical question from your everyday practice and the rapid search for an answer. The question is composed of four parts. Population is the patient population. The event is a treatment, diagnostic, screening or prognostic tool. The comparison is to a reference standard (formerly known as a gold standard, until the price dropped precipitously). The outcome is the most important part of the question and serves to focus the question. Are you interested in patient quality of life, reduction in the number and severity of migraines, accuracy of a new diagnostic test, or the cost utility of screening a population for a disorder? Some examples, of what Sackett termed the educational prescription, are:

Population	Event	Comparison (reference standard)	Outcome measure
Carpal tunnel syndrome patients	Quantitative sensory testing	Conventional nerve conduction studies	diagnostic accuracy
In patients with suspected carpal tunnel syndrome, is quantitative sensory testing as accurate as conventional nerve conduction studies?			
Closed head injury, with GCS > 13	clinical examination	MRI	morbidity due to surgically treatable lesions
In patients with a closed head injury and a GCS > 13, is the clinical examination as sensitive as MRI in reducing mortality due to surgically treatable lesions?			
Alzheimer's disease	Special care units	conventional nursing home facility	quality of life/ economic analysis
In patients with Alzheimer's disease, do special care units provide a better quality of life than conventional nursing home facilities? or In patients with Alzheimer's disease, are special care units more cost effective than conventional nursing home facilities?			
Grade one astrocytoma	chemotherapy	(radiation therapy)	prognosis
In patients with newly diagnosed grade one astrocytoma, does treatment with chemotherapy improve the prognosis? or In patients with newly diagnosed grade one astrocytoma, does treatment with chemotherapy improve the prognosis when compared to radiation therapy?			

Using educational prescriptions is an easy method to focus clinical thinking and to guide one's search. For example, let us look at the answer to the question: In patients who have had a stroke are anticoagulants or antiplatelet agents superior in reducing acute mortality and long term recurrence of stroke?

### Searching for Evidence

Searching the Cochrane Collaboration database using the term transient ischemic attack yielded 25 reviews and 3 protocols. One of the reviews provided information that oral anticoagulation does not substantially reduce the risk of stroke and increases the risk of hemorrhagic events in people without valvular problems. (Algra, De Schryver, 2002) Another review demonstrated that the antiplatelet agent, aspirin reduces the mortality in the two weeks after a stroke and reduces the risk or recurrent

stroke.(Gubitz, Sandercock,2002) Unless you subscribe to the Cochrane collaboration, you can only access the summary. Searching using Medline produced the report of AAN and AHA joint commission on the use of anticoagulant and antiplatelet therapies in acute stroke, published simultaneously in **Neurology** and **Stroke**.(Coull, Williams,2002, Coull, Williams,2002)

### Simple Statistics in EBM

A few simple statistics in EBM are necessary to understand the results of the answer to your educational prescription.

- Sensitivity =  $a / (a+b)$ . The proportion of those with the disease and abnormal tests result. Abnormal result in disease.
- Specificity =  $d / (c+d)$ . The proportion of those without disease who have a normal test results. Normal in health.
- Positive Predictive value (PPV) =  $a / (a+c)$ . The proportion of those with an abnormal result who have the disease.
- Negative Predictive value (NPV) =  $d / (b+d)$  The proportion of those with a normal result who do not have disease
- Likelihood ratio positive (LR+) =  $sens / (1-spec)$  The likelihood of any member of the study population with an abnormal result having the disease/
- Likelihood ratio negative (LR-) =  $(1-sens) / spec$  The likelihood of any member of the study population with a normal result not having the disease.
- Pre-test odds = prevalence / (1-prevalence)
- Post-test odds = pre-test odds x likelihood ratio
- Post-test probability = post-test odds / (post test odds + 1)

An example for a test is:

		Test Result		
		Abnormal	Normal	
Disease state	Disease	80 A	20 B	100 (A+B)
	Control	20 C	80 D	100 (C+D)
		100 (A+C)	100 (B+D)	

Sensitivity = 80 % (0.8)

This test accurately diagnoses 80% of the subjects who have the disease (true positive).

Specificity = 80 % (0.8)

The portion of those without the disease who will be accurately diagnosed as not having the disease (true negatives)

Pre-test probability (prevalence) = 50% (.5)

The portion of the study population with the disease.

Positive Predictive value (PPV) = 80 % (0.8)

The proportion of those with an abnormal result who have the disease.

Negative Predictive value (NPV) = 80% (0.8)

The proportion of those with a normal result who do not have the disease.

Likelihood ratio positive (LR+) = 4

Ratio of true positives to false positives. An abnormal test result is four times more likely to be associated with the disease in question than not.

Likelihood ratio negative (LR-) = .25

Ratio of false negatives to true negatives. There is a one in four chance that a negative result will occur in a subject with the disease.

Pre-test odds = 1

The chance of finding an abnormal test result before the test is run. Your chances of finding the disease based upon the total population of the study group.

Post-test odds = 2

The chance of finding an abnormal test result after the test is run.

Post-test probability = 67% (2/3)

The ratio of true positives to the rest of the study population. The diagnostic test improves the ability to diagnosis the disease by 17% (from the prevalence of 50 % to 67 %)

Other terms to be familiar with are the Odds Ratio (OR, =  $(a \times d)/(b \times c)$ ). This is the chance of a person having a disease based upon an exposure, compared to those without the exposure, or the chance of a person improving with a treatment versus another treatment.

These terms are used applying the results of your search. For example, if a test has a 93% sensitivity and an 82% specificity to detect carpal tunnel syndrome, 93 out of 100 people with the disease will have an abnormal result (7 will be missed) and 82 out of 100 people without carpal tunnel syndrome will be correctly identified by the test as being normal.

If the odds ratio of mesothelioma after exposure to asbestos is 3.3, then those who are exposed have 3.3 times the risk of developing mesothelioma than those who do not. With odds ratios it is important to understand the confidence interval. A 95% confidence interval of an odds ratio means, that is the study was repeated 100 times in a similar (but not the same) population, then 95 out of 100 times the result will be within that range. If the 95% confidence interval of an OR includes 1.0, then the exposure is as likely to cause disease as not and the OR is not significant.

## Where to Find Evidence and Guidelines

Web sites:

Medline

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>

AAN

<http://aan.com/professionals/practice/index.cfm>

Cochran Collaboration

<http://www.cochrane.org/>

Oxford Centre for Evidence

<http://minerva.minervation.com/cebm/>

Based Medicine

Rapid searching through the Internet can yield a wealth of information quickly. The National Library of Medicine's Medline indexes about 70% of clinical trials. They also index practice guideline. Using the limits option you can select Practice Guideline from

the Publication Type dialogue. The complete text of the guideline may be available through a specialty organization, like the AAN, or through the published if the host library at the University or medical center subscribes to the online version. Searching for Randomized Clinical Trials under the same dialogue box limits the search, allow you to focus the question.

When you are not fortunate enough to find that someone else has done the work for you by writing a guideline or practice parameter, then you need to look at the evidence and make your own conclusions. The search should be guided by looking at studies with the least amount of bias first. Look for randomized controlled clinical trials of the disease and intervention of interest. Read the abstract, then do not read the article. If the abstract does not contain information needed for your search, move on. If it does read part of the article, but not all of it. An article can be broken down into four parts, introduction or why it was important for the authors to do the study; methods or how they did it; results, what they found; and the discussion. The discussion is either why they found the results they wanted or why they did not. We only care about the methods and results. We skip the introduction because we know the question is important to us. We skip the discussion because we can draw our own conclusions. Later we can see if our conclusions match those of the authors. The methods tell us if the paper is relevant to our question and the results provide the information to make our own conclusions.

### **Limitations of EBM**

Bias is the introduction of systematic error into a study. In using EBM, we try to minimize or to balance the inherent bias in studies to determine an answer as close to the truth as possible. In looking at the literature, we always try to generalize the results of one study to the patient and problem at hand. In the past, a lot of research was performed on older men of European ancestry. Currently more effort is made to include women, children, and other ethnic and racial groups. Still, the results of a study are valid for that population and may not be extrapolated to all populations. One example is to plot height as a function of age for a sample of children aged three to 16 years. A linear relationship can be described using simple linear regression and height can be predicted based upon age using this formula. Can this be used to predict height of a 25-year-old or a two month old? No. We are aware of obvious biological mechanisms that increase in height stops around 16 to 18 years. The regression formula is valid only for the range of the population studies. Extrapolation can be quite misleading. In one study from Japan, 277 subjects with post herpetic neuralgia received either no treatment, or four weekly treatments with intrathecal lidocaine, or intra-theal lidocaine plus methylprednisolone, in a randomized, controlled clinical trial.(Kotani, Kushikata,2000) Two hundred and seventy of the subjects were followed for two years. While there was minimal change in pain intensity for the no treatment and intrathecal lidocaine groups, pain intensity decreased by 70% in the intrathecal lidocaine plus methylprednisolone. There was a high degree of controversy over this report, based primarily on the high success rate compared to other treatments, and the lack of benefit when this had been tried by other investigators. The bottom line is that this treatment worked as given in Japan on Japanese patients. There may be cultural and biological reasons why these findings can or cannot be generalized to other patients.

Clinical trials are designed to answer a few clear questions. As such, efforts are expended to minimize confounders when a study is designed, For example, patients with serious medical illnesses, other than the one in question will be excluded. This keeps the cost down and by minimizing confounders boosts the statistical power of the study. The more homogeneous the population the easier it is to perform the study. Clinical practice encompasses heterogeneous populations.

A common limitation of using EBM in clinical practice is lack of evidence. In the preparation of a practice parameter on the treatment of post herpetic neuralgia, I was surprised to find that there was a complete lack of controlled clinical trials using carbamazepine in this disorder. The only papers were case series, and few conclusions can be made from case series other than the data was insufficient to answer the clinical question. In a similar vein, thymectomy for Myasthenia gravis has not been studied in a randomized clinical trial.(Gronseth and Barohn,2000)

Blinding and randomization of studies of therapeutics or diagnostic techniques are preferred because of the more realistic magnitude of change reported in blinded studies. Typically, non-randomized studies overestimate the magnitude of change by 30 to 60%.(Ioannidis, Haidich,2001) In some, the overestimate may be greater. The greater the stake of the authors in the outcome, the greater the chance of bias. Reports of a new surgical technique reported by the surgeon, with no objective independent assessment are probably biased towards a positive outcome, The same could be said of large case series published by a neurologist without objective, independent assessment. Nevertheless, for some techniques and treatments, reports of blinded studies are not available. No one would argue that penicillin should be retested against a placebo, in a blinded study, as a treatment for streptococcal infection. Yet, in electrodiagnostic medicine, few of the papers used any form of blinding. Attempts to judge the accuracy of electrodiagnostic tests against reference standards are hampered by the fact that in the original reports the authors were aware of the clinical history and examination when they performed the electrodiagnostic studies. These reports met the scientific standards of their day, but future studies must meet a higher standard. To determine the efficacy of these older reports in comparison to newer techniques, the lack of blinding must be accounted for.

Guidelines are also time sensitive. The AAN practice parameter on the treatment of dementia was current at the time of acceptance by the journal.(Doody, Stevens,2001) The recommendations were limited to and based upon short-term studies of the newer medications available for Alzheimer's disease. Since publication several long-term studies have been published which show that then benefit from the current medications is best when given early in the course and that function that was lost by subjects in the placebo arms was not recovered when they were placed on open label medication.

## **Summary**

EBM is a technique that utilizes critical thinking to seek the answer to a clinical question from the literature. For some, these skills come naturally. For the rest of us, a little

instruction and guidance can guide us on the path to developing and applying these skills in our clinical practices and in providing instruction to students and house officers.

### **Resources:**

Sackett DL, Straus S, Richardson S, Rosenberg W, Haynes RB. Evidence-Based Medicine: How to Practice and Teach EBM (2nd Edition) London; Churchill Livingstone. 2000.

### **Bibliography:**

1. Algra A, De Schryver E, van Gijn J, Kappelle L, Koudstaal P. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin (Cochrane Review). [online]. Available.
2. Coull BM, Williams LS, Goldstein LB, Meschia JF, Heitzman D, Chaturvedi S, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). *Stroke* 2002;33(7):1934-1942.
3. Coull BM, Williams LS, Goldstein LB, Meschia JF, Heitzman D, Chaturvedi S, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). *Neurology* 2002;59(1):13-22.
4. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56(9):1154-1166.
5. Gronseth G, Barohn R. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:3-4.
6. Gubitz G, Sandercock P, Counsell C. Antiplatelet therapy for acute ischaemic stroke (Cochrane Review) [online]. Available.
7. Ioannidis JP, Haidich A-B, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA* 2001;286:821-830.
8. Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med* 2000;343(21):1514-1519.