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INTRODUCTION: THE PHILOSOPHY OF EVIDENCE- BASED MEDICINE

Gordon Guyatt, Brian Haynes, Roman Jaeschke,
Deborah Cook, Trisha Greenhalgh, Maureen Meade,
Lee Green, C. David Naylor, Mark Wilson, Finlay McAlister,
and W. Scott Richardson

The following EBM Working Group members also made substantive contributions to this section: Victor Montori and Heiner Bucher

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CLINICAL SCENARIO

Who's Right?

A senior resident, a junior attending physician, a senior attending physician, and an emeritus professor were discussing evidence-based medicine over lunch in a hospital cafeteria. "EBM," announced the resident with some passion, "is a revolutionary development in medical practice." She went on to describe EBM's fundamental innovations in solving patient problems. "A compelling exposition," remarked the emeritus professor. "Wait a minute," the junior attending exclaimed with some heat, and then proceeded to present an alternative position: that EBM has merely provided a set of additional tools for traditional approaches to patient care. "You make a strong and convincing case," the emeritus professor commented. "Something's wrong here," the senior attending exclaimed to her older colleague, "their positions are diametrically opposed. They can't both be right." The emeritus professor looked thoughtfully at the puzzled doctor and, with the barest hint of a smile, replied, "Come to think of it, you're right too."

Evidence-based medicine (EBM) is about solving clinical problems.¹ In 1992, we described EBM as a shift in medical paradigms.² In contrast to the traditional paradigm of medical practice, EBM acknowledges that intuition, unsystematic clinical experience, and pathophysiologic rationale are insufficient grounds for clinical decision making; and it stresses the examination of evidence from clinical research. In addition, EBM suggests that a formal set of rules must complement medical training and common sense for clinicians to interpret the results of clinical research effectively. Finally, EBM places a lower value on authority than the traditional medical paradigm does.

We continue to find this paradigm shift a valid way of conceptualizing EBM. As our opening vignette about the lunchtime conversation suggests, the world is often complex enough to invite more than one useful way of thinking about an idea or a phenomenon. In this section, we describe the way of thinking about EBM that currently appeals to us most. We explain two key principles of EBM relating to the value-laden nature of clinical decisions, along with a hierarchy of evidence. We note the additional skills necessary for optimal clinical practice, and we conclude with a discussion of the challenges facing EBM in the new millennium.

TWO FUNDAMENTAL PRINCIPLES OF EBM

As a distinctive approach to patient care, EBM involves two fundamental principles. First, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade the benefits and risks, inconvenience, and costs associated with alternative management strategies, and in doing so consider the patient's values.¹ Second, EBM posits a hierarchy of evidence to guide clinical decision making.

1. Clinical Decision Making: Evidence Is Never Enough

Picture a patient with chronic pain resulting from terminal cancer. She has come to terms with her condition, has resolved her affairs and said her goodbyes, and she wishes to receive only palliative therapy. The patient develops pneumococcal pneumonia. Now, evidence that antibiotic therapy reduces morbidity and mortality from pneumococcal pneumonia is strong. Almost all clinicians would agree, however, that even evidence this convincing does not dictate that this particular patient should receive antibiotics. Despite the fact that antibiotics might reduce symptoms and prolong the patient's life, her values are such that she would prefer a rapid and natural death.

Now envision a second patient—an 85-year-old man with severe dementia, who is incontinent, contracted, and mute, without family or friends, who spends his days in apparent discomfort. This man develops pneumococcal pneumonia. Although many clinicians would argue that those responsible for this patient's care should not administer antibiotic therapy because of his circumstances, others, by contrast, would suggest that they should do so. Again, evidence of treatment effectiveness does not automatically imply that treatment should be administered. The management decision requires a judgment about the tradeoff between risks and benefits; and because values or preferences differ, the best course of action will vary from patient to patient and among clinicians.

Finally, picture a third patient—a healthy, 30-year-old mother of two children who develops pneumococcal pneumonia. No clinician would doubt the wisdom of administering antibiotic therapy to this patient. However, this does not mean that an underlying value judgment has been unnecessary. Rather, our values are sufficiently concordant, and the benefits so overwhelm the risks, that the underlying value judgment is unapparent.

In current health care practice, judgments often reflect clinical or societal values concerning whether intervention benefits are worth the cost.² Consider the decisions regarding administration of tissue plasminogen activator (tPA) versus streptokinase to patients with acute myocardial infarction, or administration of clopidogrel versus aspirin to patients with transient ischemic attack. In both cases, evidence from large randomized trials suggests that the more expensive agents are more effective. In both cases, many authorities recommend first-line treatment with the less expensive, less effective drug, presumably because they believe society's resources would be better used in other ways. Implicitly, they are making a value or preference judgment about the tradeoff between deaths and strokes prevented, and resources spent.

By *values* and preferences, we mean the underlying processes we bring to bear in weighing what our patients and our society will gain—or lose—when we make a management decision. The explicit enumeration and balancing of benefits and risks that is central to EBM brings the underlying value judgments involved in making management decisions into bold relief.

Acknowledging that values play a role in every important patient care decision highlights our limited understanding of eliciting and incorporating societal and individual values. Health economists have played a major role in developing a science of measuring patient preferences.^{3,4} Some decision aids incorporate patient values indirectly: If patients truly understand the potential risks and benefits, their decisions will likely reflect their preferences.⁵ These developments constitute a promising start. Nevertheless, many unanswered questions remain concerning how to elicit preferences and how to incorporate them in clinical encounters already subject to crushing time pressures. Addressing these issues constitutes an enormously challenging frontier for EBM. We discuss these issues in more detail in Part 2F, “Moving From Evidence to Action, Incorporating Patient Values.”

2. A Hierarchy of Evidence

What is the nature of the “evidence” in EBM? We suggest a broad definition: any empirical observation about the apparent relation between events constitutes potential evidence. Thus, the unsystematic observations of the individual clinician constitute one source of evidence, and physiologic experiments constitute another source. Unsystematic observations can lead to profound insight, and experienced clinicians develop a healthy respect for the insights of their senior colleagues in issues of clinical observation, diagnosis, and relations with patients and colleagues. Some of these insights can be taught, yet rarely appear in the medical literature.

At the same time, unsystematic clinical observations are limited by small sample size and, more importantly, by deficiencies in human processes of making inferences.⁶ Predictions about intervention effects on clinically important outcomes based on physiologic experiments usually are right, but occasionally are disastrously wrong. We provide a number of examples of just how wrong predictions based on physiologic rationale can be in Part 2B1, “Therapy and Validity, Surprising Results of Randomized Controlled Trials.”

Given the limitations of unsystematic clinical observations and physiologic rationale, EBM suggests a hierarchy of evidence. Table 1A-1 presents a hierarchy of study designs for treatment issues; very different hierarchies are necessary for issues of diagnosis or prognosis. Clinical research goes beyond unsystematic clinical observation in providing strategies that avoid or attenuate spurious results. Because few—if any—interventions are effective in all patients, we would ideally test a treatment in a patient to whom we would like to apply that treatment. Numerous factors can lead clinicians astray as they try to interpret the results of conventional open trials of therapy. These include natural history, placebo effects, patient and health worker expectations, and the patient's desire to please.

TABLE 1A-1

A Hierarchy of Strength of Evidence for Treatment Decisions

- N of 1 randomized controlled trial
- Systematic reviews of randomized trials
- Single randomized trial
- Systematic review of observational studies addressing patient-important outcomes
- Single observational study addressing patient-important outcomes
- Physiologic studies (studies of blood pressure, cardiac output, exercise capacity, bone density, and so forth)
- Unsystematic clinical observations

The same strategies that minimize bias in conventional therapeutic trials involving multiple patients can guard against misleading results in studies involving single patients.⁷ In the N of 1 randomized controlled trial (RCT), patients undertake pairs of treatment periods in which they receive a target treatment during one period of each pair, and a placebo or alternative during the other. Patients and clinicians are blind to allocation, the order of the target and control is randomized, and patients make quantitative ratings of their symptoms during each period. The N of 1 RCT continues until both the patient and clinician conclude that the patient is, or is not, obtaining benefit from the target intervention. N of 1 RCTs are often feasible,^{8,9} can provide definitive evidence of treatment effectiveness in individual patients, and may lead to long-term differences in treatment administration (see Part 2B1, “Therapy and Validity, N of 1 Randomized Controlled Trials”).¹⁰

When considering any other source of evidence about treatment, clinicians are generalizing from results in other people to their patients, inevitably weakening inferences about treatment impact and introducing complex issues of how trial results apply to individual patients. Inferences may nevertheless be very strong if results come from a systematic review of methodologically strong RCTs with consistent results. However, inferences generally will be somewhat weaker if only a single RCT is being considered, unless it is very large and investigators have enrolled a diverse patient population (see Table 1A-1). Because observational studies may under-estimate treatment effects in an unpredictable fashion,^{11,12} their results are far less trustworthy than those of randomized trials. Physiologic studies and unsystematic clinical observations provide the weakest inferences about treatment effects.

This hierarchy is not absolute. If treatment effects are sufficiently large and consistent, for instance, observational studies may provide more compelling evidence than most RCTs. By way of example, observational studies have allowed extremely strong inferences about the efficacy of insulin in diabetic ketoacidosis or that of hip replacement in patients with debilitating hip osteoarthritis. At the same time, instances in which RCT results contradict consistent results from observational studies reinforce the need for caution. Defining the extent to which clinicians should temper the strength of their inferences when only observational studies



are available remains one of the important challenges for EBM. The challenge is particularly important given that much of the evidence regarding the harmful effects of therapies comes from observational studies.

The hierarchy implies a clear course of action for physicians addressing patient problems: they should look for the highest available evidence from the hierarchy. The hierarchy makes clear that any statement to the effect that there is no evidence addressing the effect of a particular treatment is a non sequitur. The evidence may be extremely weak—it may be the unsystematic observation of a single clinician or a generalization from physiologic studies that are related only indirectly—but there is always evidence.

Next we will briefly comment on additional skills that clinicians must master for optimal patient care and the relation of those skills to EBM.

CLINICAL SKILLS, HUMANISM, SOCIAL RESPONSIBILITY, AND EBM

The evidence-based process of resolving a clinical question will be fruitful only if the problem is formulated appropriately. One of us, a secondary care internist, developed a lesion on his lip shortly before an important presentation. He was quite concerned and, wondering if he should take acyclovir, proceeded to spend the next 2 hours searching for the highest quality evidence and reviewing the available RCTs. When he began to discuss his remaining uncertainty with his partner, an experienced dentist, she quickly cut short the discussion by exclaiming, “But, my dear, that isn’t herpes!”

This story illustrates the necessity of obtaining the correct diagnosis before seeking and applying research evidence in practice, the value of extensive clinical experience, and the fallibility of clinical judgment. The essential skills of obtaining a history and conducting a physical examination and the astute formulation of the clinical problem come only with thorough background training and extensive clinical experience. The clinician makes use of evidence-based reasoning—applying the likelihood ratios associated with positive or negative physical findings, for instance—to interpret the results of the history and physical examination. Clinical expertise is further required to define the relevant treatment options before examining the evidence regarding the expected benefits and risks of those options.

Finally, clinicians rely on their expertise to define features that have an impact on the generalizability of the results to the individual patient. We have noted that, except when clinicians have conducted N of 1 RCTs, they are attempting to generalize (or, one might say, particularize) results obtained in other patients to the individual patient before them. The clinician must judge the extent to which differences in treatment (local surgical expertise or the possibility of patient noncompliance, for instance), the availability of monitoring, or patient characteristics (such as age, comorbidity, or concomitant treatment) may impact estimates of benefit and risk that come from the published literature.

Thus, knowing the tools of evidence-based practice is necessary but not sufficient for delivering the highest quality of patient care. In addition to clinical expertise, the clinician requires compassion, sensitive listening skills, and broad perspectives from the humanities and social sciences. These attributes allow understanding of patients' illnesses in the context of their experience, personalities, and cultures. The sensitive understanding of the patient links to evidence-based practice in a number of ways. For some patients, incorporation of patient values for major decisions will mean a full enumeration of the possible benefits, risks, and inconvenience associated with alternative management strategies that are relevant to the particular patient. For some of these patients and problems, this discussion should involve the patients' family. For other problems—the discussion of screening with prostate-specific antigen with older male patients, for instance—attempts to involve other family members might violate strong cultural norms.

Many patients are uncomfortable with an explicit discussion of benefits and risks, and they object to having what they perceive as excessive responsibility for decision making being placed on their shoulders.¹³ In such patients, who would tell us they want the physician to make the decision on their behalf, the physician's responsibility is to develop insight to ensure that choices will be consistent with patients' values and preferences. Understanding and implementing the sort of decision-making process patients desire and effectively communicating the information they need requires skills in understanding the patient's narrative and the person behind that narrative.^{14,15} A continuing challenge for EBM—and for medicine in general—will be to better integrate the new science of clinical medicine with the time-honored craft of caring for the sick.

Ideally, evidence-based technical skills and humane perspective will lead physicians to become effective advocates for their patients both in the direct context of the health system in which they work and in broader health policy issues. Most physicians see their role as focusing on health care interventions for their patients. Even when they consider preventive therapy, they focus on individual patient behavior. However, we consider this focus to be too narrow.

Observational studies have documented the strong and consistent association between socioeconomic status and health. Societal health is associated more strongly with income gradients than with the total wealth of the society. In other words, the overall health of the populace tends to be higher in poorer countries with a relatively equitable distribution of wealth than in richer countries with larger disparities between rich and poor. These considerations suggest that physicians concerned about the health of their patients as a group, or about the health of the community, should consider how they might contribute to reducing poverty.

Observational studies have shown a strong and consistent association between pollution levels and respiratory and cardiovascular health. Physicians seeing patients with chronic obstructive pulmonary disease will suggest that they stop smoking. But should physicians also be concerned with the polluted air that patients are breathing? We believe they should.



ADDITIONAL CHALLENGES FOR EBM

In 1992, we identified skills necessary for evidence-based practice. These included the ability to precisely define a patient problem and to ascertain what information is required to resolve the problem, conduct an efficient search of the literature, select the best of the relevant studies, apply rules of evidence to determine their validity, extract the clinical message, and apply it to the patient problem as the skills necessary for evidence-based practice.¹ To these skills we would now add an understanding of how the patient's values impact the balance between advantages and disadvantages of the available management options and the ability to appropriately involve the patient in the decision.

A further decade of experience with EBM has not changed the biggest challenge to evidence-based practice: time limitation. Fortunately, new resources to assist clinicians are available and the pace of innovation is rapid. One can consider a classification of information sources that comes with a mnemonic device, 4S: the individual study or studies, the systematic review of all the available studies on a given problem, a synopsis of individual studies or systematic reviews or both, and systems of information. By systems we mean summaries that link a number of synopses related to the care of a particular patient problem (for example, acute upper gastrointestinal bleeding) or type of patient (for example, an outpatient with diabetes) (Table 1A-2). Evidence-based selection and summarization is becoming increasingly available at each level (see Part 1A1, "Finding the Evidence").

TABLE 1A-2

A Hierarchy of Preprocessed Evidence

Studies	Preprocessing involves selecting only those studies that are both highly relevant and characterized by study designs that minimize bias and thus permit a high strength of inference.
Systematic Reviews	Systematic reviews provide clinicians with an overview of all of the evidence addressing a focused clinical question.
Synopses	Synopses of individual studies or of systematic reviews encapsulate the key methodologic details and results required to apply the evidence to individual patient care.
Systems	Practice guidelines, clinical pathways, or evidence-based textbook summaries of a clinical area provide the clinician with much of the information needed to guide the care of individual patients.

This book deals primarily with decision making at the level of the individual patient. Evidence-based approaches can also inform health policy making,¹⁶ day-to-day decisions in public health, and systems-level decisions such as those facing hospital managers. In each of these arenas, EBM can support the appropriate goal of gaining the greatest health benefit from limited resources. On the other hand, evidence—as an ideology, rather than a focus for reasoned debate—has been

used as a justification for many agendas in health care, ranging from crude cost cutting to the promotion of extremely expensive technologies with minimal marginal returns.

In the policy arena, dealing with differing values poses even more challenges than in the arena of individual patient care. Should we restrict ourselves to alternative resource allocation within a fixed pool of health care resources, or should we be trading off health care services against, for instance, lower tax rates for individuals or lower health care costs for corporations? How should we deal with the large body of observational studies suggesting that social and economic factors may have a larger impact on the health of populations than health care delivery? How should we deal with the tension between what may be best for a person and what may be optimal for the society of which that person is a member? The debate about such issues is at the heart of evidence-based health policy making, but, inevitably, it has implications for decision making at the individual patient level.

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