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Evidence-Based Medicine – Perspectives of a Community-Based Pediatrician

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1. Introduction

Have we succumbed to a new tyranny in medicine—evidence-based medicine? With apologies to my former professor, Dr. David Sackett! but has the randomized controlled trial (RCT) become a new idol? Indeed, EBM has been satirized as a new religion.¹ At the risk of not being 'politically correct',² I would argue that evidence-based medicine (EBM) can be abused and substituted for sound clinical judgment. The exponents of the new paradigm we call evidence-based medicine recognized this: "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."³ Evidence-based medicine, when properly understood and applied, improves patient outcomes but it is often misunderstood and used inappropriately.⁴ It is important to recognize the limitations of EBM as well as its benefits in the care of our patients. Strauss and McAlister point out some of the limitations of EBM⁵: "shortage of coherent, consistent scientific evidence, difficulties in applying evidence to the care of individual patients, barriers to the practice of high-quality medicine, limited time and resources, paucity of evidence that evidence-based medicine works." One common example that many community generalists would share around the concept of 'barriers to the practice of high-quality medicine' is the issue of a lack of resources for the appropriate care of one's patient. For example, there is an unacceptable waiting time for a child you suspect of having autism to see a child psychiatrist to confirm the diagnosis and enable the family to obtain publicly funded resources for early intervention. This is equally true for other psychiatric disorders. Indeed, the wait time for many subspecialties in pediatrics is often in the order of many months.

Evidence-based medicine is an offshoot of the philosophical movement known as scientific positivism. Scientific positivism is a particular philosophy, which states that only that which is scientifically verifiable is true. The critique of scientific positivism is that its central premise is itself not scientifically verifiable but must be accepted as a sort of first principle or axiom. Similarly, the principle of evidence-based medicine must be itself accepted as an

axiom of the system. This can be seen if we frame the following question, 'what is the evidence that evidence-based medicine improves patient outcomes?' In fact, there is no such evidence since such a trial would be extremely difficult and unethical to do. "Evidence-based medicine, like other models of care, has limitations ...efforts need to be directed toward ... conducting studies to test whether and how evidence-based medicine affects processes of care and patient outcomes."⁶

Let me clearly state that my comments are not to be taken as an excuse to return to magical thinking or charlatanism. The outstanding achievements of modern medicine have been accomplished through the rigorous application of the scientific method in developing evidence-based guidelines. Patient outcomes have certainly improved with the application of these treatments. We are also aware of therapeutic disasters when the principles of controlled observations and rigorous research designs are not observed. (eg tying off the internal mammary arteries in the treatment for angina pectoris⁷).

Having said this, there is an *a priori* reason why we should not substitute evidence-based medicine for a more holistic approach and that is quite simply that the evidence is never complete. This is a fundamental feature of the scientific method and it is applicable in all the sciences. Recently, for example, the most fundamental aspect of Einstein's theory of special relativity, the fixed speed of light (299,792,458 m/sec) has been challenged by experiments at OPERA which demonstrated that neutrinos travel slightly faster than the speed of light.⁸ If this finding is duplicated by other laboratories, then our understanding of the fundamental features of space-time will need to be revised. Until this announcement, it was unthinkable that Einstein's constant was not true since his theory of special relativity made many predictions subsequently validated by observation. However, this latest challenge to Einstein should not surprise us because the basic hermeneutic underlying the scientific method depends on theories *validated by observations*; as the observations change through more and more sophisticated technological advances, the theories need to be modified. Physicists have yet to achieve the unifying theory which combines Einstein's theory of special relativity and quantum mechanics which at present are incompatible. Evidence-based medicine is based on the scientific method and it is subject to the same caveats as physics and cosmology. Theoretically, the evidence base will continue to unfold *ad infinitum* since there is no principle which enables us to know that the end of the evidence has been reached and there can be no further evidence. We can only act in the concrete world of sick patients with the evidence at hand, as best as it, knowing that perhaps further evidence will prove us wrong.

A recent discussion in the New England Journal of Medicine highlights this problem and introduces a new dynamic.⁹ The authors relate the case of a 13 year-old girl with lupus erythematosus with nephritic syndrome, antiphospholipid antibodies and pancreatitis. They cite the difficulty of knowing whether or not to anticoagulate this patient since there is no data in the pediatric literature on this question. There would also be the danger of inducing bleeding. A survey of other pediatric rheumatologists did not produce a consensus. Since there were no RCT's on this question, the authors state that they turned to their hospital's EMR database and within the space of a few hours obtained their experience over the previous five years to arrive at an 'electronic cohort'. Through this retrospective analysis

they opted to treat their patient with anticoagulants. This was not a RCT of anticoagulants versus no anticoagulants in a selected group of patients with SLE but physicians using their judgment based on past experience. “Did we make the correct decision for our patient? Thrombosis did not develop, and the patient did not have any sequelae related to her anticoagulation; truthfully, though, we may never really know. We will, however, know that we made the decision on the basis of the best data available—acting...in the light of experience guided by intelligence.”¹⁰

There is always the possibility of newer evidence that will invalidate a particular diagnosis, therapeutic choice or diagnostic test. Newer diagnostic tools inevitably result in a greater understanding of pathophysiology, e.g. the explosion of molecular genetics. Often, there is no definitive RCT in the literature to help one with a clinical decision. Sometimes the results of a Cochrane summary, i.e. the evaluation of available RCT's regarding a particular question, are contradictory or inconclusive.¹¹ One could also argue that the ‘gold standard’ RCT is best used when a clearly defined therapy is being tested i.e. drug A vs drug B in a well-defined group of patients. This may be the case in a secondary or tertiary care center but is not the case in primary care where multiple pathologies may be at work in a broader group of patients. An RCT may not be the most useful tool when evaluating problems in primary care where there is a less highly selected group of patients with a single defined etiology.¹² The outcome measure used in an RCT may be inappropriate as in the case of rosiglitazone where the primary outcome measure was the lowering of glycated hemoglobin. The clinical trials leading up to the release of this drug on the markets focused on an outcome that may not be relevant (glycemic control) and ignored important side effects, assuming that a reduction in glycated hemoglobin translates into improved patient outcome. Indeed the side effects (weight gain, edema, and changes in lipids) detected during the clinical trials may well be more important with regard to outcome than glycemic control. Nissen and Wolski in fact showed that rosiglitazone increases the risks of myocardial infarction, despite improved glycemic control.¹³

Recently, Ioannidis has argued cogently that much published research is eventually shown to be false. This results from the attempts to achieve a conclusive result based on a single study assessed statistically using a p value of $<.05$. “A finding from a well-conducted, adequately powered randomized controlled trial starting with a 50% pre-study chance that the intervention is effective is eventually true about 85% of the time. ...Conversely, a meta-analytic finding from inconclusive studies where pooling is used to “correct” the low power of single studies, is probably false if $R < 1:3$. Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present.”¹⁴ There is also a darker side to the quest for evidence-based guidelines when vital evidence is withheld from the public domain, or falsified, invalidating the ‘evidence’ upon which a particular therapy is recommended. An example of this occurred with the clinical trials of a new iron-chelator, deferiprone. Apotex, the pharmaceutical firm developing the new drug, would not allow the publication of negative data. While researching a new iron-chelating agent, deferiprone, for Apotex, Nancy Olivieri of the Hospital for Sick Children in Toronto, uncovered data indicating that the drug would not provide long-term control of iron overload in patients with thalassemia major and worsened hepatic fibrosis. The pharmaceutical firm funding her research, Apotex, would not allow her to publish the data

because of a research contract. Dr. Olivieri published the data regardless¹⁵ and a major controversy regarding academic freedom ensued at great personal cost to Dr. Olivieri.¹⁶ Another example is that of the COX-2 inhibitors. In the enthusiasm to release a new drug, rofecoxib, a COX-2 inhibitor, Bombardier et al¹⁷ overlooked an important cardiovascular side effect in a subgroup of patients even though the drug showed promise in the group of patients for which the clinical trial was designed, those with rheumatoid arthritis. Subsequent analysis of the data indicating a substantial risk for cardiovascular events in patients taking the drug, resulted in the withdrawal of rofecoxib (Vioxx) from the market. . This has recently led to the institution of a registry for all RCT's; any researcher who wishes to publish in any of the major medical journals will now have to insure that their RCT is registered in the public domain, with all data both positive and negative available.¹⁸

There is also the moral issue of using data from trials conducted unethically as in the infamous Tuskegee Syphilis study in which 399 poor black sharecroppers were denied effective treatment so that researchers could follow the natural history of syphilis.¹⁹ Similar comments can be made about the Nazi doctors and the use of eponyms such as Hallervorden-Spatz syndrome, honouring a pathologist, Hallervorden, who actively participated in the Nazi euthanasia program in order to obtain specimens of human brains for his research.²⁰

Evidence can be published in recognized medical journals that is false because it has been unethically manipulated to justify a particular conclusion. Such was the case of the unjustified link between MMR immunization and autism published in *The Lancet* by Dr. Andrew Wakefield.²¹ This publication was not only wrong but the data was manipulated as was shown by Brian Deer's exposé published in the *British Medical Journal* in 2011.²² Wakefield postulated that 12 children had a 'new syndrome' of enterocolitis and regressive autism. In fact, 3/12 patients did not have regressive autism. 5/12 had a previous diagnosis of developmental problems long before receiving MMR vaccine and the symptoms of autism occurred months after the MMR was given and not within days. The study was further biased by the fact that the patients were recruited by known anti-MMR campaigners. Furthermore Dr. Wakefield stood to make financial gain through litigation by suing the pharmaceutical firms manufacturing the vaccine if his 'research' was generally accepted. The *Lancet* subsequently retracted the article in 2010 after untold damage had been done.²³ The false link between MMR and autism has caused needless worry to parents and along with other factors has led to a decline in herd immunity to measles with resultant increase in the number of cases in the developed world, where previously measles had almost been eliminated. As of October 2011, 26,074 cases of measles have been reported in European member states, with 14,000 cases in France alone. This has resulted in 7288 hospitalizations and 9 deaths.²⁴ Thus, while evidence-based practice is desirable, it is not always possible because of contamination of the evidence by either incomplete or changing evidence, and unethical manipulation of evidence. Because of these failures, evidence-based medicine cannot always lead to the healing and relief from suffering that our patients seek. Paradoxically, they turn to complementary and alternative medicine (CAM) which often has less of an evidence base than traditional medicine.

A further issue is that conclusions drawn from RCT's are based on a statistical assessment of the participants in the clinical trial but you must apply the conclusion to your particular

patient. The danger is that your particular patient may not be similar to the patients in the clinical trial. This is especially a problem when trying to apply the results of a study, which has been done in a secondary or tertiary care center. The patients enrolled in such a trial may be quite different than the patients seen in a community practice. At any given clinical encounter, the physician does not have all the information needed to make an evidence-based decision. For example, every individual patient has a particular pharmacogenetic profile, which is largely unknown. Another major problem in pediatrics is, of course, that most drugs are 'orphans' i.e. there is no good information derived from studies in pediatrics and so we 'extrapolate' from adult studies. It is good to remind oneself that 'extrapolation' means that we are outside the principle of evidence-based medicine – we are extrapolating or going beyond the evidence on an assumption. The assumption is that what holds true for adult patients will hold true for pediatric patients. Of course, the 'assumption' is not evidence-based! Moreover, we now know that this assumption is often untrue. Consequently, evidence-based principles sometimes 'break down' in the concrete world in which individual physicians must act.

The renowned mediaeval philosopher/theologian Thomas Aquinas made a distinction, derived from Aristotle, between the speculative and practical intellect. The speculative intellect is the locus of analytical, theoretical thinking and this is the home of evidence-based medicine. The practical intellect, however, is the locus of applying evidence-based medicine to the practice of medicine: the specific judgment (having taken into account the evidence and the particulars of this patient before me) that the physician makes in determining the appropriateness of a particular treatment. The practical intellect is the final common pathway leading to a particular judgment for a particular patient. Let us take an example. A 9 year old girl is brought to your office at 5:00 PM on a Friday afternoon complaining of an earache. You correctly diagnose an otitis media. Evidence-based medicine would suggest that the correct course is not to prescribe an antibiotic but rather to prescribe analgesics and re-examine the patient 48 hours later; if no resolution, then it is appropriate to prescribe an antibiotic. But other considerations may override the principles of evidence-based medicine: the mother may not be able to come back for a re-examination or the family is about to catch a plane for a holiday etc. Thus, a more holistic approach is mandated and the principle of evidence-based medicine breaks down. There is always a certain unpredictability in our encounters with patients.

Let us take another example. There are many excellent pediatric hospitals that care for patients with cystic fibrosis. A recent article in *The New Yorker* describes how all of them follow the same evidence-based guidelines for the treatment of cystic fibrosis and yet if one examines their results, they are distributed along a bell curve; most of the hospitals were only average in their results and one hospital stood out: the Babies and Children's Hospital in Cleveland where a respirologist named LeRoy Matthews had established a program for the treatment of cystic fibrosis in 1957. When national mortality rates for cystic fibrosis in the best centers was around 20%, Matthews claimed that his mortality rate was less than 2%. What was the difference? The difference turned out to be innovation and constantly challenging the evidence-based guidelines which record past experience.²⁵ We must remain focused on our patients and challenge ourselves to do better, to go beyond the evidence-based guidelines in order to excel, thereby constantly improving the guidelines themselves.

A recent essay in the New England Journal of Medicine entitled, *The New Language of Medicine* argues that we are in danger of losing the notion that physicians are healers. We now refer to ourselves as 'providers' who have a 'product' to sell and our patients are now 'consumers' buying this product. "Beyond introducing new words, the movement toward industrializing and standardizing all of medicine (rather than just safety and emergency protocols) has caused certain terms that were critical to our medical education to all but disappear. 'Clinical judgment', for instance, is a phrase that has fallen into disgrace, replaced by 'evidence-based practice', the practice of medicine based on scientific data. But evidence is not new; throughout our medical education beginning more than three decades ago, we regularly examined the scientific evidence for our clinical practices. On rounds or in clinical conferences, doctors debated the design and results of numerous research studies. But the exercise of clinical judgment, which permitted assessment of those data and the application of study results to an individual patient, was seen as the acme of professional practice."²⁶

In conclusion, there have always been two streams in medicine: the Hippocratic and Aesculapian. Evidence-based medicine and guidelines belong to the Hippocratic stream. The Aesculapian stream emphasizes healing and the importance of the psychological and spiritual aspects involved in healing. Because physicians do not always take this into account, many patients turn to complementary medicine for relief of their symptoms. Modern 21st Century medicine needs to be reminded of both the Hippocratic and the Aesculapian heritage in its long and renowned history. A good physician must take a holistic approach in any clinical encounter with a suffering human being. *Evidence-based medicine must never be abandoned* but it must be incorporated into the practical intellect along with the particular concrete aspects of *this patient* in order to make an appropriate and efficacious therapeutic decision. The cornerstones of caring for our patients and practicing good medicine are the encounter with the patient through our history and physical examination. We then combine this with the principles of evidence-based medicine, recognizing its hermeneutic weakness, to arrive at the best possible outcome for our patient. It is then that evidence-based medicine becomes "'ebullience-based medicine,' a lively, enthusiastic, continually joyful expression of our good fortune at having the privilege to be able to care for and advocate for children."²⁷

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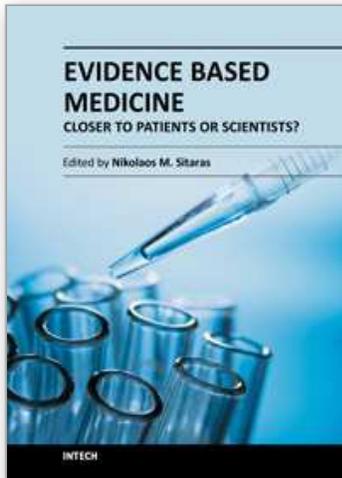
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Evidence-based medicine (EBM) was introduced to the best benefit of the patient. It has transformed the pathophysiological approach to the outcome approach of today's treatments. Disease-oriented to patient-oriented medicine. And, for some, daily medical practice from patient oriented to case oriented medicine. Evidence has changed the paternalistic way of medical practice. And gave room to patients, who show a tendency towards partnership. Although EBM has introduced a different way of thinking in the day to day medical practice, there is plenty of space for implementation and improvement. This book is meant to provoke the thinker towards the unlimited borders of caring for the patient.

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