

Evidence-Based Medicine

Part 2: Evidence and the Introduction of New Therapies into Practice

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Abstract

This is the second of a two-part series discussing evidence-based medicine and its role in medicine today. In the previous article, we explored some of the shortcomings of RCTs and argued that other kinds of evidence, such as pathophysiology and clinical judgement, are an important piece of the puzzle. Such evidence may be especially critical where RCTs are not available for the treatment in question. In the present article, we focus on a particular instance where RCTs are virtually never available, and that is the area of emerging or “experimental” therapies. We delineate criteria that, if satisfied, may guide the physician to more strongly consider a new therapy despite insufficient evidence and apply this scheme to the examples of cardiac transplantation and HIV vaccination.

Introduction

When a patient requires medical care, health care providers must decide which therapy or therapies to offer. This decision is complex and may be influenced by many contributing factors, such as institutional policy, availability of therapies, marketing by commercial companies, cost/benefit to the patient, the preferences of the patient or the patient’s caregivers, financial cost, the health care provider’s personal experience with the therapy, a physician’s desire for recognition or money, medical-legal concerns, the need to conform to the practices of colleagues, and what the scientific evidence shows to be most effective. In recent years, an increasing focus on this final point has encouraged an explosion in the medical literature, administration, and education of evidence-based medicine (EBM). The EBM doctrine has focussed on the efficacy of the treatment in guiding practice and it has considered randomized controlled trials (RCTs) to be the gold standard in informing clinical decisions on treatment.¹ However, in the case of a novel therapy, the lack of “high quality” evidence can make it difficult to decide on whether to use the treatment or not. Therefore, the question arises of whether to prescribe or refrain from offering the treatment because it has not yet been “proven” effective. Herein lies the dilemma we will attempt to address in this article. We discuss the manner by which novel therapies enter

practice before their efficacy is firmly established. Next, we delineate criteria that, if satisfied, may guide the physician to more strongly consider a new therapy. Finally, we apply this scheme to the examples of cardiac transplantation and HIV vaccination.

“Desperate patients argue that technology assessment takes too long – it isn’t fair to patients or physician-scientists to have to wait in the face of life-threatening illnesses.”²

In the case of emerging therapies, evidence is lacking almost by definition. Such novel technologies as prenatal surgery, gene therapy, and new AIDS drugs or cancer treatments, may be labeled as “experimental” or “cutting edge”, but what they frequently have in common is that evidence supporting their effectiveness is scant. Rarely does the evidence include RCTs, because they are time consuming and expensive to perform, as well as impractical for therapies which are at such an early stage of development.^{3,4} Evidence must also be lacking when physicians and surgeons devise new and creative solutions to the clinical problems with which they are faced on a day-to-day basis. Consequently, in these situations, physicians must make decisions on whether to offer the treatment on the basis of what evidence is available, including pathophysiological evidence, clinical experience, and animal or human studies. Grimes points out that, “as physicians, we are ethically bound to be sure that tests, procedures, and treatments we provide are worth the money, pain and inconvenience they cost.”⁵ This fact notwithstanding, when faced with these decisions, physicians often choose the new technology.⁵ Table 1 lists just a few examples of treatments that entered common practice before rigorous scientific evaluation.

Many authors see it as a failing of past and current medical practice that treatments should be applied to patients without “proof” of efficacy; one author writes: “technologies continue to be introduced without thorough, well-designed evaluations . . . we should be critical consumers of the evaluation process”.¹⁰ However, David Sackett, one of the fathers of the EBM movement, acknowledges that one may proceed in the absence of RCTs in certain cases:

“Because the randomized trial, and especially the systematic review of several randomized trials, is so much more likely to inform us and so much less likely to mislead us, it has become the “gold standard” for judging whether a treatment does more good than harm. *However, some questions about therapy do not require randomized trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted.* And if no randomized trial has been carried out for *our* patient’s predicament, we must follow the trail to the next best external evidence and work from there.”¹

Table 1
“Unproven” Technologies that
Entered Common Medical Practice

Technology/application	Reference
• Primary prevention of coronary disease by treatment of hypertriglyceridaemia in diabetics	6
• Lung volume reduction surgery (LVRS) in emphysema	7-9
• PCR for diagnosis of HIV infection	10
• Military anti-shock trousers (MAST) in posttraumatic hypotension	3, 10, 11
• Norepinephrine, hypertonic saline and crystalloid in posttraumatic hypotension	11
• Occluder devices for patent ductus arteriosus	2
• Mother’s 24-hour urine estriol as an index of fetal health	5
• Postcoital test and sperm penetration assay in infertile couples	5
• Electronic fetal monitoring	5
• Bloodletting in obstetrics	
• Episiotomies in vaginal deliveries	5
• Radial keratotomy for refractive errors of the eye	5

In fact, as Dickens points out, as far as the law is concerned, novelty alone does not make a procedure experimental. A physician’s innovation is considered non-experimental if no orthodox treatment exists or if orthodox treatments have become discredited.¹² Innovation is crucial to the advancement of medical science, and “without innovation, . . . surgical evolution will grind to a halt.”¹³ In surgery, high quality care for each patient necessitates constant minor refinements and adaptations of well-recognized techniques, and therefore it is important for the surgeon to be able to innovate without requiring an RCT every step of the way. Put another way, “the absence of evidence of effectiveness is not the same as absence of effectiveness.”¹⁴ Moreover, premature studies of efficacy of a budding therapeutic advance inhibit maturation of the therapy and carry the risk of rejecting a treatment that requires further refinements before becoming efficacious. With the advent of genetic profiling, therapy may become increasingly individualized,

and hence less supportable (experiments with an *n* of 1). Therefore, there may be some circumstances in which it is entirely appropriate for a therapy to enter practice without large RCTs that prove its efficacy.

Consequently, we believe that a physician may adopt a technology before full scientific assessment has occurred if he or she feels that the therapy is more effective than the available evidence shows, and if the possible benefits of its use outweigh the risks. This view is in contrast to Grimes, who offers only cynical explanations, complaining of the “uncritical acceptance of new technologies” and describing several barriers to their critical assessment:⁵

1. The prestige of proponents of the new technology sways others to adopt it also;
2. Physicians may be lured by the novelty and profitability of new gadgets and procedures;
3. The inertia of old ideas is a powerful driving force in medical practice;
4. “Pursuit of pedantry in medical education” (Grimes feels that medical students are filled with useless knowledge, rather than being taught to be scientific in their approach);
5. Uncontrolled clinical impressions may result in biased and distorted viewpoints.

Although we may be scientifically and legally justified in adopting a new treatment prior to proof of efficacy being established, this does not imply we will always be correct. In hindsight, some of the technologies listed in Table 1 are still viewed as effective (e.g. LVRS, ductus occluders), but others were shown to be useless or even harmful (e.g. MAST, bloodletting). Some authors have focussed on the latter two situations, medical “mistakes” on a large scale, to provide justification for always requiring proof of efficacy of technologies prior to widespread adoption. Nevertheless, errors may be inevitable. As paradigms change, study results that were initially judged to support a therapy may be reinterpreted. With time and further study, specific patient populations to whom the therapy has been applied will be found to be unsuitable candidates for the therapy. Sometimes, despite our best efforts to detect adverse effects beforehand, drugs or other treatment modalities can have unexpected, exotic and temporally distant effects which only become evident after the fact. Consider the likelihood of an RCT finding the vaginal clear cell carcinomas in the children of mothers treated with diethylstilbestrol (DES), for example. Therefore, rather than focussing our energies on preventing all mistakes, it may be more valuable to identify a process by which the chances of adopting successful treatments are maximized and harm arising from treatments adopted in error is minimized.

Criteria to Assist in Deciding Whether or Not to Offer New Therapy

In order to minimize the chances of adopting a useless or harmful treatment, it is useful to consider general criteria that, if met, would support early introduction of the treatment (see Table 2). These criteria can be broken down into two general categories: those that indicate a lower risk of applying the technology (Part A) and those that imply a higher risk associated with not applying it

(Part B). If a particular treatment satisfies most of these criteria, this results in a situation where there is little to lose and much to gain from the technology's immediate application and conversely, if most of the criteria are not met, there is much to lose and little to gain.

Table 2
Optimal Criteria for Early Application of New Treatment

(A) Risk of applying the new treatment is low

1. pathophysiology of disease/condition is well understood and non-controversial
2. mechanism of action of treatment is well understood and non-controversial
3. proposed treatment is similar to other existing treatments
4. few and minor known or conceivable side effects or adverse reactions
5. "higher quality" evidence
6. treatment is cheap

(B) Risk of not applying the new treatment is high

1. high mortality / morbidity of disease
2. rapid disease progression
3. no effective alternative treatment or significant controversy with regards to alternative treatment or discredited "orthodox" treatment
4. existing treatment has high risks or side effects
5. existing treatment is expensive

Although Table 2 does not provide a quantitative or numerical assessment of the risks, the structured approach may be of value in thinking about this issue. Based on the extent to which these criteria are met, that is, one's assessment of the risks associated with applying the new treatment versus not applying it, we can define four states (see Table 3) that describe varying degrees of support for the introduction of a new treatment. Next, we discuss two examples, one historical and one current, in order to illustrate the application of these concepts.

Table 3
Decision Matrix Based on Risk Assessment

		Risk of not applying the new treatment	
		High	Low
Risk of applying the new treatment	High	Evaluate carefully; possible indication to wait	Clear indication to wait
	Low	Optimal: good indication to proceed	Evaluate carefully; possible indication to proceed

Cardiac Transplantation for CHF

*"A randomized trial has been viewed as ethically unacceptable because one of the principles of such trials is that there is genuine uncertainty about the comparative therapeutic merits of each arm in a clinical trial"*¹⁶

Heart transplantation is quite commonly used to remedy the effects of congestive heart failure (CHF). Despite a history of rigorous testing, heart transplantation surgery has not undergone an RCT.¹⁶ This historical example will serve to illustrate the rationale for standardizing an intervention without the best evidence.

History

The first transplants involving vascular anastomoses were practiced on dogs by Alexis Carrel.¹⁷ Subsequently, Vladimir Dimikhov transplanted auxiliary hearts into dog chests. Further progress was made in transplantation following the development of the heart lung bypass machine and the use of hypothermia to cool the heart during operation. The University of Mississippi heart transplantation team did the first transplant in 1964 using a chimpanzee heart on a human.¹⁷ The operation failed one hour later, as the patient's new heart could not sustain the venous return of human circulation. On Dec. 3, 1967, Christian Barnard transplanted a human heart into a human. On the eighteenth post-operative day, the patient died of pneumonia. The introduction of the immunosuppressant cyclosporin A revolutionized transplantation by preventing graft rejection and dramatically improving prognosis.

The Risk of Waiting for RCTs for Cardiac Transplantation was High

Patients with chronic heart failure in general have high mortality rates.¹⁶ Mortality depends on the degree of risk associated with the condition: those at higher risk are in more dire need of transplantation. Deng *et al* divided cardiac patients into three categories and showed that global mortality following one year of waiting was 51%, 32%, and 29% for the high, medium, and low-risk groups (both before and after transplantation), respectively.¹⁶ For those on the waiting list itself, 20% of the high-risk patients died in two months, while 32% died within a year. The need for effective therapy for CHF is clear.

The progression of heart disease to more serious states of morbidity or death has a variable time course. Certain individuals rapidly succumb to their condition, while others may survive with medical management for many years. A disease that progresses rapidly warrants quicker and more aggressive intervention than one with a more protracted natural history. In this case, the variable progression of heart disease necessitates treatment that takes into account the patients who decline most quickly.

Initially, following the advent of cyclosporin A, there were no treatments as clinically efficacious as heart transplantation,¹⁷ although no RCT was done to prove this. However, alternative treatments have come a long way. Pharmacological alternatives, including carvedilol (β -blocker) and enalapril (ACE inhibitor), improve prognosis far more than earlier therapies.¹⁸⁻¹⁹ Non-pharmacological alternatives include left ventricular assist devices and left ventricular volume reduction.²⁰ In a recent prospective obser-

vational study, Deng *et al.* showed that cardiac transplantation is beneficial only for high-risk patients on waiting lists.¹⁶ This finding, combined with the gain in popularity of other interventions, suggests that an RCT is now warranted.

The Risk of Proceeding with Transplantation was Relatively Low

The first attempted therapeutic heart transplant in 1967 followed a history of rigorous testing in both primate and non-primate models.¹⁷ Drugs aimed at preventing graft rejection were tested both *in vivo* and *in vitro*. The efforts of Carrell, Mann and Dimikhov opened the door for human transplantation. Furthermore, not only was the surgery well understood, but so too was the pathology of CHF. Taken together, these two points made transplantation seem quite promising. However, little was known of the potential side effects, and the understanding of graft rejection was primitive at the time.¹⁷ With the use of cyclosporin A, however, the risk of heart transplantation dropped significantly due to decreased rejection.¹⁶

Was an RCT Required?

According to our paradigm, cardiac transplantation for patients with severe CHF may not have required an RCT at the time of its initial introduction. The high mortality and potentially rapid progression of the disease, coupled with the lack of effective alternatives, implied great risk to not performing the surgery, while the reasonable level of knowledge about transplantation reduced the unknown risks. Withholding transplantation from the control group in such an RCT would have been unethical. Satchithananda *et al.* argue that an RCT is inappropriate even now.²¹ One group showed improved physical and psychological dimensions following transplantation, with improvements lasting up to 5 years.²² Today, with the introduction of newer effective therapies, an RCT comparing these treatments to heart transplantation might be in order.

HIV Vaccination

HIV vaccination has recently been the source of fierce debate and controversy. On one side of the debate are those optimistic about the potential preventative power this vaccine may have against one of the most deadly epidemics of our time. On the other side are those who foresee the potential danger of introducing viral antigens by means of a viral vector. One reason for the debate is that drug treatments for AIDS are improving. Currently, highly active anti-retroviral therapies (HAART) that combine protease inhibitors, such as saquinavir, and nucleoside reverse transcriptase inhibitors, such as zidovudine and lamivudine, are effectively improving survival and lowering HIV RNA in the plasma.²³ In contrast, vaccination has not consistently shown the same efficacy to date.²⁴⁻²⁵ If it could be proven in animal models that the vaccine conferred immunity to the HIV virus, the issue would become even more complicated. Should the vaccine be widely administered in places where the prevalence of HIV is high, or should public health officials wait for the results of RCTs before administering the vaccine? This hypothetical example based on a current issue illustrates the difficulty in deciding when to proceed with treatment in the absence of evidence.

The Risk of Waiting for RCTs is Intermediate

The HIV/AIDS epidemic is proliferating boundlessly: the number of cases reached 36 million in 2000, with sub-Saharan Africa being especially affected.²⁶ An estimated 5 million new cases and 3 million deaths were reported that same year.²⁶ Current preventative measures have done little to control the virus.²⁵ These chilling facts provide support that a vaccine, once developed, should be used as soon as possible. However, the progression of AIDS is relatively slow, ranging anywhere from a few months to several years before the onset of symptoms. There are also strong treatment regimens available with HAART.

The Risk of Proceeding with Vaccination is Intermediate

The underlying premise of vaccination is the introduction of viral antigens in either a viral vector, such as canarypox, or a non-viral vector.²⁵ Although the canarypox viral vector does not replicate in mammals, there is considerable speculation that the virus may “replicate in vaccinated individuals, causing disseminated disease.”²⁴ Future plans in vaccination include using live attenuated HIV viruses to induce a host immune response. Random incorporation into the host genome can lead to cancers and may also produce replication competent viruses.²⁵

Are RCTs Required?

Ethical and scientific barriers complicate the administration of trials for HIV vaccination.²⁷ Some argue that such studies use people in third world countries as “guinea pigs” and are therefore unethical.²⁴ The scientific concerns outlined above call into question the safety of using viral vectors in priming and boosting the immune system to defend against subsequent infections.²⁴ This is, however, the very reason why trials are so important for this particular treatment modality. The scientific uncertainty behind the vaccination must be resolved prior to the vaccine’s widespread dissemination. Although the vaccination has the potential to save the millions of people that are infected yearly, this knowledge is tempered by the fact that there is an unknown risk of detrimental complications in the much larger number of people who would be vaccinated. On the other hand, some researchers contend that with the use of such vectors as the canarypox virus, safety is nearly guaranteed. With the number of casualties to AIDS reaching three million and the number of new cases also in the millions, it may be worth considering implementing the vaccine prior to the arrival of RCT results. The situation posed by HIV is a complicated one that reminds us that even with a set of criteria, the burden of implementing treatments without evidence of efficacy and safety is immense.

Conflicting Principles: Do the Most Good vs. Do No Harm

“Primum non nocere” (above all, do no harm) is an often-quoted tenet in medicine. However, it implies an absurd consequence: since all effective treatment contains some element of risk, to be certain of doing no harm, one must do nothing. Therefore, when we give any drug for which any serious adverse drug reactions are reported, or perform any procedure with a chance of mortality, we attempt to do the most good and the least harm. By analyzing the risks and benefits inherent to the treatment, we try to selectively apply our interventions so that over time, more will be helped than

harmful. When the outcomes of our methods are not incompletely studied and may not be known for years, many people who might have been helped by the new treatment will not benefit if we wait for those studies. On the other hand, the risk of adopting the new treatment is inadvertent harm to patients. Therefore, this decision-making scheme is intended to provide a strategy to help guide us in terms of when to act and when to wait so as to cause the greatest good and least harm.

Conclusion

As physicians, we must be conscious and cautious of our acceptance of new treatment modalities by critically evaluating the evidence. Sometimes, it may be appropriate to implement a novel, unproven, or experimental treatment in the patient's best therapeutic interest, despite the relative lack of evidence in the medical literature of its efficacy. We have established criteria that may help guide when such action is more or less supported. The ultimate goal of this decision-making framework is to try to provide the most good, by providing rapid access to useful therapies, while attempting to minimize wastage or harm due to the adoption of useless or harmful practices. As part of this framework, it must be acknowledged that errors are inextricably linked with the uncertainty and continuous advancement of medical science. As such, the adoption of some harmful practices is inevitable and acceptable, so long as the process by which they were adopted was reasonable. When a novel treatment enters practice, testing should occur simultaneously; major innovations should be "made the object of formal research at an early stage to determine whether they are safe and effective."²⁸

When physicians discuss treatment with patients, they might do well to refrain from categorizing therapeutic options as "experimental" or "standard" treatment. No evidence is absolute truth, and no truth is certain; therapies fall on a continuum with varying degrees of support. When we acknowledge this fact, we can see that the distinction between the two is to some extent arbitrary. Without labels, what we are left with is the need to be knowledgeable and open and to explain the nature of each treatment choice, the amount of experience with it, and the evidence of its risks and likelihood of success that has been amassed from that experience. Such discussions promote more critical views in the physician and go much further towards promoting patient autonomy.

"The history of medicine is a graveyard of failed ideas."³ Occasionally, patients will come to harm as a result of these failed ideas. This must be balanced against the good that ultimately results from the successful ones.

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