



SPOTLIGHT EXPERT ROUNDTABLE

The Role of Experience in an Evidence-Based Practice

Discussants: **Gordon Guyatt, MD¹; Mark Tonelli, MD²**

TMR: Drs. Gordon Guyatt and Mark Tonelli were invited to participate in this Expert Roundtable Discussion to address how they see the role of expert opinion changing in the evolving framework of the now outmoded “evidence-based hierarchy” popularized over the past 20 years (See Figure). Their discussion highlights certain aspects of the current Evidence-Based Medicine (EBM) conceptualizations and thinking. Dr. Gordon Guyatt is a distinguished professor in the Department of Clinical Epidemi-

ology & Biostatistics and a member of the Department of Medicine at McMaster University in Hamilton, Ontario, has been writing and publishing on EBM for decades, and is a leader in the cutting edge discussion on the new Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines (see Additional Reading) for rating the quality of evidence.

Dr. Mark Tonelli is from the University of Washington Medical Center, Seattle, Washington, where he is a professor in the Division of Pulmonary and Critical Care Medicine, and adjunct professor of Bioethics and Humanities as well as the program director of the Pulmonary and Critical Care Medicine Fellowship. He has also been writing and publishing on EBM for decades, primarily regarding the limits of EBM for clinical practice and the value of experience in clinical decision-making (See Table). They discuss their ideas, thoughts and concerns in this Expert Roundtable.

DR. GUYATT: I think there are three principles of evidence-based health care: one is that some evidence is more credible, more believable.

We have more confidence in some types of evidence than others. Second, we need systematic summaries of the highest-quality evidence available. And, thirdly, evidence by itself never tells you what to do. It's always evidence in the context of values and preferences.

If I understand it, Dr. Tonelli, your criticisms have tended to focus on the first of those three principles.

DR. TONELLI: I think that is correct. I would agree with you on the third principle absolutely. But let me start by saying that we need to be clear what we mean by evidence, as that term is used in a variety of ways. I think, in particular, if we're talking about the results of clinical research as evidence, that clinical research itself is never sufficient for clinical decision making. Patient values and preferences are important, but I think other topics are also important, some of which you've acknowledged before. The individual circumstances of a case determine whether clinical research is applicable.

So, while I agree with your third statement, I disagree with the first,

ABSTRACT

The discussion focused primarily on: 1) A critical evaluation of the value of evidence-based healthcare and the role it plays in patient centered medicine; 2) the three main principles of evidence-based healthcare; 3) the role that clinical research should play in clinical decisions; 4) the importance of patient values and preferences; 5) the value of personal “hands on” experiences and pathophysiologic reasoning; 6) balancing clinical experience and pathophysiologic rationale with the results from clinical trials; 7) customizing clinical decisions based on the individual patient; 8) the NEW GRADE framework for evaluating the quality of evidence beyond traditional outmoded EBM. *Med Roundtable Gen Med Ed* 2012;1(1):75-84.

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From McMaster University, Hamilton, Ontario, Canada¹; University of Washington Medical Center, Seattle, WA²

Address for correspondence: Gordon Guyatt, MD, McMaster University, 1280 Main Street West, Rm. 2C12, Hamilton, Ontario, Canada L8S 4K1. Email: guyatt@mcmaster.ca

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which I think supports the notion that there is a hierarchy of evidence, particularly one that would apply to clinical practice. But in fact, sometimes the randomized control trial is not more compelling than personal experience or pathophysiologic reasoning in clinical decision making.

DR. GUYATT: I think it would be good to define the boundaries of our agreement and disagreement. Let me tell you three situations quickly and you can tell me whether you agree with the way the medical community has responded, because, to me, it does suggest something of a hierarchy. So, 20 years or so ago, the cerebrovascular surgeons were doing extracranial to intracranial bypass surgery for middle cerebral artery narrowing. Their personal experience was that patients did extremely well with this, much better than they used to, and they had a compelling physiologic rationale for it.

Randomized trials were subsequently performed and suggested that there was no benefit, and, in fact, some harm, associated with the usual complications of the surgery. More recently, encainide and flecainide were two drugs that virtually obliterated asymptomatic arrhythmias. The cardiologists' experience with it was excellent. They had a very powerful physiologic rationale that even persuaded the Food and Drug Administration to license the drugs before randomized trials. The randomized trials were still performed, and encainide and flecainide were found to increase rather than decrease arrhythmic deaths.

Finally, when I was training in medicine, when you had a patient with heart failure, beta-blockers were contraindicated with again a compelling physiologic rationale and clinical experience. Thirty years later, randomized trials have suggested that they are the most powerful agent we have in terms of reducing mortality in patients with heart failure. So, in those three instances, we had clinical experience

and physiologic rationale that suggested one course of action, and randomized trials that suggested another. The clinical community seems to believe that the randomized trials have trumped the physiologic rationale and clinical experience and I wonder whether you would agree.

DR. TONELLI: I would agree with that. I think those are three examples that show up a lot in this debate, the Cardiac Arrhythmia Suppression Trial (CAST) in particular,¹ that people like to use to say that mechanistic reasoning or pathophysiologic rationale is untrustworthy. I think those randomized controlled trials were well designed to answer the question of whether or not the interventions should be routine care, do they actually produce the benefits we think they do. Those are all appropriate and informative studies. In fact, I argued vehemently years ago that lung volume reduction surgery, which had both the pathophysiologic rationale and some local clinical experience in

St. Louis, should be the subject of a large controlled study, because you do not want to routinely provide a service that doesn't benefit patients.²

So, in answering those questions, I agree. The randomized controlled trials are very helpful.

I want to switch the perspective, though, because I think it's very important to understand my concerns about an individual clinician who's facing a decision about the care of an individual patient disregarding pathophysiologic rationale and clinical experience in deference to clinical research. I do intensive care unit (ICU) medicine, so I'm sorry that those are going to be a lot of my examples. For instance, low tidal-volume ventilation for acute respiratory distress syndrome, has been demonstrated to be beneficial in large, randomized trials, and yet the patient in front of us may not be responding in a way that we would expect. There may be profound hypoxemia that I can correct with a small increase in tidal volume, and I would say I'm going to disregard, or at least put aside for the moment, the results of excellent studies that suggest I use 6 mL/kg tidal volume in this patient, and I'm going to go up to 8. Otherwise I cannot oxygenate this patient and this patient is going to die or this patient is having arrhythmias that go away when I do that. So, the perspective that I'm arguing from is that of the clinician, who should be able to still use pathophysiologic rationale and personal experience in making decisions about individual patients. I am not talking about public health policy decisions, where I

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agree with you that such policy decisions are often well-informed by randomized controlled trials.

DR. GUYATT: Well, as I suspected, I think the disagreements between us are perhaps relatively minor and a matter of emphasis, but we'll continue to see. So, first of all, to the extent that you don't agree with the hierarchy of evidence, in certain instances at least, it seems that you do believe in a hierarchy. In the situations we introduced earlier, you believed that when you had physiologic rationale and clinical experience that was contradicted by the results of clinical trials, the clinical trials do at least in some of those circumstances trump the prior clinical experience and physiologic reasoning.

DR. TONELLI:

I agreed that in some situations, both in clinical practice and more broadly, clinical research will be more compelling than a pathophysiologic argument or personal experience, but that in no way actually suggests a hierarchy because I don't think in all cases that a randomized controlled trial trumps pathophysiologic reasoning or clinical experience. In fact, there are multiple examples, as you're well aware, of initial randomized controlled trials that seem to suggest that an intervention is beneficial where often there were pathophysiologic or experiential concerns that, low and behold, long-term, turns out that that intervention is not beneficial. I think activated protein C in patients with sepsis is a classic example of that. So, just because there are examples where pathophysiologic reasoning has not won

out over randomized controlled trials, there are also times when randomized controlled trials subsequently are demonstrated through other empiric research to have been misleading and that people who voice the concerns based on pathophysiology and experience were raising appropriate concerns.

DR. GUYATT: Well, two things with respect to the example. We're just about to have a paper published in the *British Medical Journal*³ that suggests that the reasons for the concerns

previous trials that have been done, with a prior probability that single interventions for sepsis were highly unlikely to be beneficial. I do think that clinicians' background knowledge plays a big role in how they interpret findings, particularly individual pieces of clinical research.

DR. GUYATT: There was at least disagreement about the physiologic rationale. Certainly the company that spent a lot of money developing the drug believed there was an underlying physiologic rationale, but at any rate, it seems to me that maybe we have a semantic disagreement. First of all, I'd agree that there are many reasons not to trust randomized trial findings, especially early trials of an intervention. A lot of my current writing is about reasons not to trust

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over activated protein C should have been that the trials were stopped early for benefit. So, there may have been, and to my understanding there were, many people—and tell me if you disagree with this—there were a number of prior agents that were used, and there were many people within the intensive care unit community, a lot of disappointment with the ultimate trial that showed that it was of no benefit, who found the physiologic rationale behind the use of activated protein C very compelling.

DR. TONELLI: I wouldn't say that a lot of people found it compelling. I think that the physiologic rationale behind it was, for many of us, minimally supportive, and in fact, as you point out, I think a lot of us looked at that first trial, looking at all of the

randomized trials, and the GRADE framework⁴ that I've helped develop identifies categories of problems including imprecision, inconsistency, indirectness in terms of applicability to the population, which I think is something that you would emphasize, along with publication bias as well as risk of bias. We've written, as I alluded to earlier, about the big problem of stopping trials early and about early results that are too good to be true.

So, for sure, there are lots of reasons to be skeptical about the results of randomized trials, but it seems to me that we perhaps have a semantic disagreement about what we mean by a hierarchy. There's at least a collection of circumstances in which when they come head-to-

head, it seems that you agree that the results of randomized trials would trump prior physiologic reasoning and clinical experience and you seem to make the case that since it doesn't always do that, that you're unready to call it a hierarchy. It seems to me that since it very often does that when put head-to-head, I'd be ready to call it a hierarchy. So, perhaps it is a subtle semantic distinction we have here.

DR. TONELLI: I think maybe a little beyond that. There are a couple of other reasons why I think the hierarchy doesn't make sense. One is that I think when we talk about clinical research and pathophysiologic rationale and personal experience that those are three different types of medical knowledge, not variations of the same thing. So, they can't really be placed in a hierarchy. I do think there are some times when the randomized control trial clearly doesn't trump my pathophysiologic reasoning. For instance, a study of homeopathy that suggests that it's beneficial or a study of retroactive intercessory prayer that suggests that it's beneficial is just not going to be compelling. Those studies are not going to overcome my pathophysiologic understanding of how illness works.

Since each of the three types of medical knowledge is different in kind, they don't belong on a hierarchy. What clinicians are left with in caring for individual patients is trying to consider each of those types of knowledge and weighing them. Sometimes the clinical research is very compelling and other times it is not. Frankly, quite often, as I think both of us would agree, these things line up nicely. Our personal experience, our pathophysiologic understanding, and the clinical research, all line up and it's very compelling, making decision making easy.

It's those times when they don't that I have a concern with a hierarchy. The idea that a poorly done observational trial should trump my personal experience every time, I don't think is a reasonable argument.

DR. GUYATT: I'm still thinking that the disagreements are relatively minor. So, for certain you have to look at all the evidence and each clinician's clinical experience is a form of evidence, and the better documented that clinical experience, the more it would be appropriate to have confidence in it and as we bring in safeguards against bias, then our confidence increases further. So, clinical experience is a form of evidence and all clinical research is the systematic application of clinical observation with safeguards against bias.

So, I think we'd agree, you have to look at all the evidence and perhaps another way of putting our hierarchy is that—you alluded to one example where you were calling for randomized trials—in many situations, we need randomized trials to resolve uncertainties. That implicitly acknowledges that in at least some instances, what we would call evidence lower in the hierarchy, you may say it's not lower in the hierarchy but it is at least unsatisfactory in resolving the issue, we call in randomized trials to resolve such situations.

DR. TONELLI: I agree. I think it's very important to make sure that we frame the question before we ask how best to answer it. I do think that, as many people acknowledge, there are certain beliefs in medicine where we are completely convinced by pathophysiologic rationale, in which we don't need randomized control trials at this point in time to answer. The value of antibiotics for severe pneumonia, for instance. There are other situations where, frankly, experience and pathophysiologic ratio-

nale is not compelling and we need to do something else to answer that question. The question in those situations is generally a very broad one. The question is, is this the best approach as a matter of routine? Is this the best intervention for a particular class of patients?

I think the other difficulty for evidence-based health care is that when we're asking a question about a particular patient, the patient who's in front of us, if we're asking what's the best thing to do for Mr. Jones, that question is not going to be answerable by an appeal to a randomized controlled trial. Then, that necessitates that we bring in a variety of types of medical knowledge, and, as you've acknowledged and I clearly recognize, also the patient's experiences and goals and values into that decision-making process. So, we first have to understand, what is the question. When the question is about what is best for a particular patient, a randomized controlled trial is not going to answer that question.

DR. GUYATT: Let me understand what you're saying. Let's assume we had someone who clearly fits the eligibility criteria of a particular body of evidence, multiple trials appropriately summarized in a systematic review and meta-analysis that give the optimal evidence, that leave us quite confident of the desirable and undesirable consequences of the intervention. Why wouldn't the results be applicable to the individual?

DR. TONELLI: I think the question for the clinician is always, are they applicable and is there something about this particular individual that would make me concerned that they're not applicable? That might be something that the study didn't take into account or wasn't part of the inclusion or exclusion criteria. Certainly, I think you would acknowledge that it could

be that the patient doesn't value the outcome of the trial.

So, it doesn't make sense to apply that intervention. It may be that there's something about what I'm able to provide in this locality that may impact the decision. So, there are still issues that need to be considered about whether those study results are going to be compelling enough to determine the care for this patient. It's never, and I think you would agree, that one can simply directly and deductively apply the results of even a body of evidence to an individual patient.

DR. GUYATT: I would translate what you're saying not as you can not apply the results of a body of evidence to a particular patient but rather that before you apply the results of a body to a patient, you should make sure that in fact it's appropriate to apply to that individual. You've stated it very nicely. You have a body of evidence and you start out by saying, is there something about this individual that would make it unlikely or that would make me have serious questions that the results from this body of evidence do in fact apply to the individual?

Secondly, you may then ask whether there is something about our situation and circumstance that although, if we were in the right setting, the results would apply to our patient, something about our setting means that we cannot apply the intervention as it was done in the studies or something else peculiar about the setting makes us hesitate. I agree we should always do that. And third, which you point out, again, very appropriately, I would frame it a little bit differently. You would say the results don't apply to the patient because the patient puts a very low value on the beneficial outcomes that were identified and puts a high value on inconvenience or burden associated with the intervention.

I would argue that the results still apply to the patient. They give us our best estimate of the desirable and undesirable consequences, and the way to apply it to the patient is that we can show the results to the patient and the patient can say, that applies to me, but I am not interested now that I understand the best estimates of the desirable and undesirable consequences. The way I'd reframe what you said is you have to ask the question of whether these results can be applied to the individual because of the characteristics of the patient or the setting. Then, if the answer is yes, you have to ask, how can the results best be interpreted in the context of this particular patient's values and preferences? The answer may frequently be yes. It applies very directly to the patient. It gives the best estimates of what we can expect in this individual and then you go about applying values and preferences.

DR. GUYATT: I'll give my summary, but then you might give a different account. We have established that there are instances in which randomized trials are needed to resolve issues where uncertainty exists as a result of prior evidence and clinical experience and physiologic reasoning, and we also agree that one needs to be skeptical about the results of randomized trials, and that prior knowledge bears on how we will interpret the results of randomized trials. I am more inclined to say that it is worth thinking about this as a hierarchy and Dr. Tonelli much less inclined to say it is worth thinking about as a hierarchy.

We agree that anytime you have the results of a randomized trial, applying that to an individual patient should not be done as an automatic process. Rather, it is necessary to take a serious look asking, is there some way the results are not applicable to this patient? Is there something about the

setting that makes the results not applicable to the situation, and then the context in terms of the patient's values and preferences, that the results may be interpreted very differently in treating one patient and not another because of differences in values and preferences? I'd be inclined to characterize the situation that the results of trials are often directly applicable to the patients, but that applicability should always be questioned seriously, and you are more inclined to characterize it as the results, the trials are never applicable to individuals. Dr. Tonelli, correct me where I've gone astray.

DR. TONELLI: I never said that the results of clinical trials are never applicable or are never informative. That would be an indefensible position. What I said is that clinical research can never be directly or deductively applied to individual patients. That this has to be an active process that incorporates other forms of medical knowledge.

I think I view it a little differently than you do. In the User's Guide you describe a sequential process as opposed to the more complex reasoning that I think occurs. The role of the individual physician is to take into account both the clinical research and anything about this particular individual that may be different in terms of physiology or some aspect of the clinician's experience that suggests that this patient may not respond in a way that clinical evidence would suggest. I think it's the role of the physician as well to elicit and put into context the patient's experiences and their goals and values and understand the system's features that are relevant to the decision. I believe that's all one step. It's not a sequential process.

The clinician is going to come to some conclusion about what is probably the best course of action for this

individual patient. I think that there is an important distinction here, that the focus throughout the entire process is really on this particular individual. What clinical research you bring into it depends on the individual as opposed to looking at the individual and then heading out into the world of published randomized controlled trials to try to see which one is most appropriate to bring back. So, I do think we both acknowledge that clinical research is not directly applicable to the care of an individual patient. There needs to be some process, although I think we disagree a little bit on what that process looks like.

DR. GUYATT: Seeing the way you put it there, I'm not sure that there's anything I would disagree with, but let me clarify—at the end you said that there is a problem with taking the patient, defining the patient's problems and then going and seeking the best available evidence. Did I misunderstand you? Is there something wrong with saying okay, here is the patient and here's the patient's problem? Here are the alternatives we are considering to deliver optimal care. I better be aware of the best available evidence that bears on what the effects of the intervention are likely to be in this patient.

DR. TONELLI: No, I don't disagree with that. I think one better be aware of what clinical research could be relevant to a particular decision. I think what I'm trying to point out is that there is this subtle distinction between looking at a patient and framing a question, a general question, that can be answered by going to the clinical research and then applying that back to the patient. Does that make sense? Because what I don't want to do when I'm dealing with individuals is to define a general question.

The question before the clinician is still, what is best to do for this par-

ticular patient? What's the best thing to do for Mrs. Jones? Not necessarily, what's the best thing to do for a patient who's had a previous myocardial infarction and has diabetes and is now presenting with worsening heart failure. That general question is more easily answerable by going to the medical literature, but it takes me one step away from what the real question is, which is, what's the best thing to do for this particular patient?

DR. GUYATT: See what you think of this. The way we frame it is as a way of helping clinicians go through the process and, as we have agreed, the clinician needs to find, and understand the best available evidence to apply to the individual. So, let's assume in our paradigmatic situations, we say the clinician suspects she doesn't know the best evidence that's available and concludes she better find out.

If one is talking about enabling or helping or making optimal the physician's process, we believe that it is extremely helpful to start out with a structured clinical question that is the first step in entering into the search for the optimal information. I often teach people to frame their question: for instance, a 60-year-old hypertensive, hyperlipidemic, nondiabetic man, that's our patient. Well, if we demand only studies that include patients with all those characteristics, we know in advance we aren't going to find any studies. That's probably not the most helpful way of doing it.

So, let's pick the key characteristics of the individual to define our patients that would make it likely that we'll actually find some systematically conducted evidence that bears on the patient, and similarly with the intervention, comparators, and outcomes. One then goes out having constructed a question in that way,

finds the best evidence, and then comes back with the issue of the applicability. So, it turns out that what we find is more or, perhaps as you point out, less applicable to the individual, and the evidence from formal studies in the literature then provides indirect evidence with respect to this individual. Yes, it may apply, but no, it may not.

Then, you need to make a decision considering the uncertainty that has been generated by these issues of applicability. So, if we're framing it as a sequence, it is designed for the situation when the clinician is uncertain of what the best evidence available is and needs to be systematic about going about attaining that evidence and then applying it back to the patient.

DR. TONELLI: I think we would agree that in modern medical practice that it's an absolute necessity for optimal practice that clinicians be aware of what relevant clinical research has to say about issues pertinent to individual patients. I think the process that you describe in terms of how one might go about that is certainly one reasonable approach. My hope, again, when we talk about taking care of individual patients, is that most clinicians will be able to bring into the physician-patient relationship that information without having to go through this entire process. Maybe that's more likely for some specialists than generalists, I don't know, but certainly you want physicians to be able to bring that information into the deliberation. It's an important element, but then you still need to be able to, as you note, start looking at issues around other characteristics of the individual, whether they're pathophysiologic or things that the clinician believes based on experience may be relevant to the question at hand and try to weigh those.

I think that's a challenging process, that aspect of clinical judgment and, in terms of emphasis, I think that the evidence-based medicine movement has emphasized the process you've described. Again, I'm not stating that it's unimportant or that one need not be able to understand the clinical research, but a lot of emphasis has been on the clinical research, understanding it and critically appraising it. Very little attention has been given to how individual clinicians can appropriately make these decisions when caring for particular patients, how the other types of features factor in. As you say, you acknowledge that they're important, but we haven't spent a lot of time talking about how that works and how clinicians can do it better.

DR. GUYATT: Well, I would argue that if I look back at our writings, and perhaps it's a historical phenomenon, in the first decade of evidence-based practice, that might be true, but subsequently, we've written a lot about the issues of applicability and gone back to talk about the situations of patients—what sort of patient differences, what sort of intervention, what sort of outcome differences you might take into consideration with respect, for instance, to surrogate outcomes. So, maybe we still haven't got the optimal balance, but I would also ask, who's done better in terms of writing about the real challenges of saying, here is what the published evidence, the formal research evidence, shows. What exactly should this process be? How can we provide guides for clinicians in doing the applicability exercise, the importance of which you, in my mind, completely appropriately laid out?

DR. TONELLI: Two things. First, I agree with you that the notion of EBM in practice has clearly evolved over time and, as you note, a very different focus over the past several years has emerged than over the initial 10

years where other forms of medical knowledge were actively deemphasized by evidence-based medicine. I agree with that evolution and I think that's very appropriate. I think in particular there are thoughtful proponents of the EBM who, like yourself, really get this and are interested in trying to help clinicians with that difficult issue.

Second, I think there are many other people who write about this from other perspectives, from a patient-centered medicine or a person-centered medicine approach who are particularly interested in ways to incorporate patient experience, goals, and values, into the clinician's decision-making process. Frankly, I think there hasn't been a lot of attention on trying to define for clinicians what are legitimate reasons, for instance, to not follow a practice guideline or what are illegitimate reasons not to follow a practice guideline and trying to lay that out. I think that's a lot of the work going forward.

You mentioned GRADE earlier, and I think in terms of guideline development, GRADE has clearly started to say look, there are things that are important that go beyond the study design in terms of the strength of

a recommendation. I think clinical practice is one step further away from guideline development and adds layers of complexity that you cannot account for when you're doing guidelines, and I hope to see that this discussion continues to move closer to the clinician. I do think that there are a variety of features of clinical research that make that research more or less compelling to clinicians and we should really be discussing which of those are legitimate and which are illegitimate and how we can help clinicians with this decision-making process. The critical care community has begun thinking about these questions.⁵

A related challenge for evidence-based medicine centers on helping clinicians to decide what to do with patients who would never have been eligible for a clinical trial, perhaps because of age or co-morbidities. Your thoughts?

DR. GUYATT: Well, two things. Number one, you would have to have—as you have pointed out—a question that is foremost in individual's minds when they look at the formal research evidence that there may be reasons not to apply it to the individual and that the patient may not exactly meet the

Clinical Implications

- ▶ Evidence based healthcare is a valuable tool, if it is applied in the context of patient values and patient preferences
- ▶ Physicians need to critically evaluate clinical trials based on clinical experience and physiologic rationale
- ▶ Clinical trials, while critical to the advancement of patient care, tell us about the “average” patient, while the clinician needs to apply the data to the “individual” patient by adding clinical experience
- ▶ The original EBM Hierarchy is outmoded and new systems are being developed such as GRADE guidelines

eligibility criteria is very important. We think that there has been excessive skepticism in that when you look for subgroup effects within the body of evidence that does exist, within a meta-analysis situation, for instance, different trials will have varying eligibility criteria. There are actually very few instances of subgroup effects that have been substantiated.

So, as it turns out, there are certainly instances in which this is not true, but there are many instances in which some characteristic of the patient that kept them out of the trials will not actually influence the magnitude of the patient's response to treatment. I think you would support this, what you need to look at is physiologic rationale and your understanding of the individual's physiology. The trial was conducted in Caucasians, but is atherosclerosis really different in non-Caucasians so that baseline risk may differ? Is the relative effect of the treatment going to differ?

Yes, the trial enrolled people up to 65 and our patient is 66, but is the physiology of the 66-year-old really that different from the physiology of the 65-year-old and so on? So, yes, it's important to think about, but we think clinicians would be best served by a starting point of saying, yes it is applicable, and then finding reasons to challenge that, and if there is compelling physiologic rationale, then one loses confidence and then the next thing is to say, okay, what then is the best rationale—once we have lost confidence, we're less confident—what are the implications of this loss of confidence in the management of the patient?

DR. TONELLI: I think I would largely agree with that. I think that with any set of clinical research, we're always trying to see how informative that is for a particular patient and we're forced to ask these questions. Again,

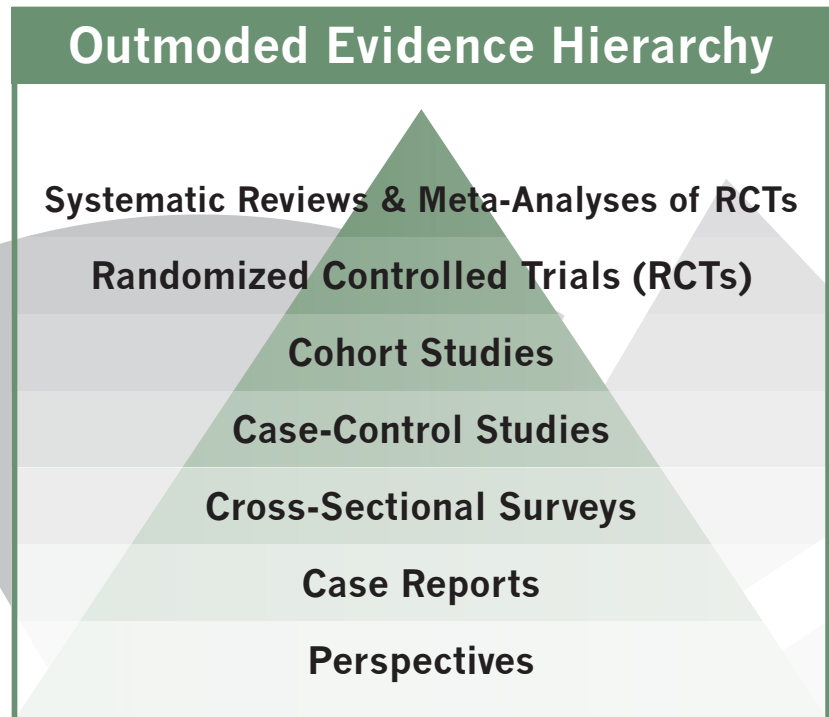


Figure. While many "evidence hierarchy" charts such as the example above were once well accepted showing the "best evidence" at the top and the "weakest" at the bottom, they are now anachronistic, and newer systems such as GRADE are gaining ground as the field evolves.

throwing out the information from clinical research simply because the patient in front of us would have met some exclusion criteria does not seem appropriate. Instead, one has to ask whether the information from the research is relevant to this patient, often from a physiologic stance.

I think the other problem related to this issue is the idea that when we start to have patients who unfortunately, for instance, have a large number of comorbidities for which there are evidence-based guidelines regarding "best practice." Such to the point that you have a patient who, if we followed the guidelines, would be on 15 or 18 medications and we start to wonder if that is really the best care because the studies often exclude patients with comorbidities and yet we know patients have multiple diseases.

I think that's another space where the clinician is then forced to say, wait

a minute, and, along with the patient's input, what are the priorities here? What are we trying to accomplish? We're not going to be able to follow all of these guidelines. That's going to cause more harm than good. So, what do we opt into and what do we opt out of? I think that's a related challenge.

DR. GUYATT: I completely agree with that and perhaps, ironically, my perception is that it's the leaders of the EBM movement who, in contrast to content area experts, are saying, wait a minute here, we need to consider what is the burden we are placing on the patient's life as in the dramatic situation just depicted regarding 15 different medications taken at different times of day and lifestyle changes we want the patient to make and everything else we want the patient to do. I believe we have taken the lead in pointing out the role of values and preferences and the fact that this may not be at all in the patient's best interest.

DR. TONELLI: I guess the takeaway points from my perspective are that clinicians recognize that the question they're trying to answer revolves around the individual patient they're dealing with and that they are required to incorporate medical knowledge from clinical research, from their personal experience, and from pathophysiologic understanding into their calculation about what is likely best for the patient. The physician also bears the responsibility of bringing in the patient's experiences, goals, and values, and the local systems features into that process. I assert that there is no hierarchy of evidence for individual clinical decisions and that physicians should not make the mistake of believing that clinical research always trumps their pathophysiologic understanding or their experience.

DR. GUYATT: I will agree. What Dr. Tonelli has just said captures very much the way the evidence-based practice community currently thinks about these things, and when we are teaching it, one of the mantras we have for people teaching evidence-based practices is start with the patient, finish with the patient. In the interval, what is included is a journey through understanding the best available evidence, which is sometimes challenging, and we spend a lot of our time and energy guiding people on how to do that. Nevertheless, as Dr. Tonelli has just expressed, there is a necessity of starting with the patient, finishing with the patient.

Table. NON-HIERARCHICAL DECISION MAKING—AREAS TO CONSIDER

The Universe of Decision Making (in alphabetical order)	
A. Clinical experience	Derived from expert opinion and/or personal clinical experience
B. Pathophysiologic rationale	Based on underlying theories of physiology, disease, and healing
C. Patient values and preferences	Derived from personal interaction with individual patients
D. Results of clinical research	Empirical results published in the medical literature
E. System features	Including resource availability, societal, religious, and professional values, legal and cultural concerns

Areas A, B and D: "... represent distinct forms of knowledge, differing in kind from one another. Each has particular strengths and weaknesses when applied to clinical decisions. Since they differ in kind, they cannot be ranked or placed in a hierarchy," Tonelli MR. *Ann 1st Super Sanita*. 2011;47(1):26-30;27.

Modified from Tonelli MR. Integrating evidence into clinical practice: an alternative to evidence-based medicine approaches. *J Eval Clin Prac*. 2006;12(3):248-256.

The only area where there is some disagreement, and I actually don't think this agreement is conceptual, would have to do with what is most useful. Is it useful to highlight the fact that there are situations, many situations, in which the study designs that guard against risk of bias will lead to stronger inferences than study designs that don't guard against risk of bias and unsystematic clinical observations that don't guard against risk of bias? Is it useful to point out to people that, in general, the situations where risk of bias is less leave us more confident than situations in which risk of bias is greater. This implies a hierarchy. We continue to think

that this is a useful way of thinking about it while we would fully acknowledge that randomized trials can often be misleading, and, as I said earlier, a lot of our current energy is in pointing out those sort of situations.

DR. TONELLI: I think that those statements summarize the discussion well. I agree that it is the individual patient who is the focus, and would also agree with one of the points from earlier on in the discussion that "beneficent" skepticism is not misleading people but is just a prompt to assess the evidence for yourself with the patient in front of you as the focus.

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ADDITIONAL READING

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