

## A Fever of Unknown Source

### **Physicians should use evidence-based guidelines as a starting point to make sound clinical treatment decisions for a patient's individual medical needs.**

Commentary by Francis Neelon, MD, Robert H. Pantell, MD, and Timothy E. Quill, MD

Mr. and Mrs. Kendall were quite excited about the newest addition to their family, 2-month-old Janna. But they were anxious on this trip to the doctor. Janna had developed a fever in the middle of the night, and the Kendalls decided to take her to the emergency room. Dr. Stinton, the ER physician on service, heard of the Kendalls' story and decided she'd better see their daughter straight away.

Upon questioning, Dr. Stinton learned that Mrs. Kendall's pregnancy with Janna was perfectly normal, as was her delivery at just over 38 weeks. In fact, until last night, the Kendalls had little reason to be concerned about Janna's health. As they reported, she'd passed all her doctor's visits with flying colors and had begun immunizations according to schedule. In other words, she was overall a healthy infant.

Last night, however, they awoke to cries unlike those they had heard before and ran in to check on Janna. She had no interest in being fed and seemed warm to her mother. She had been irritable throughout the day and less interested in nursing. Mrs. Kendall took Janna's temperature twice rectally, and both times it read 38.3° C. That's when they bundled her up and went to the ER.

On physical exam, Janna was alert and active in her mother's arms, but appeared ill. Her temperature registered 38.4° C. The physical was normal, revealing no obvious foci of infection. A complete blood count in the ER uncovered a slightly elevated white blood cell count (15.5 x 10<sup>9</sup> cells / Liter) but no other abnormalities. On the basis of these findings, Janna was admitted to the hospital for fever of unknown source; her workup included urinalysis, urine culture, chest radiography, blood cultures, and lumbar puncture. In lieu of lab results, antibiotics were started.

Distressed by the invasiveness of the tests (which lasted well into the early morning hours) and the hospital admission, the Kendalls asked for more information about the likelihood of a serious illness. Dr. Stinton responded that it was hard to say. "The information is quite complex, and we don't want to confuse you. Let's not take any chances." Willing to do whatever it took for Janna to be well, they agreed.

After Janna reached the hospital ward, Mr. Alstadt, a medical student on his clinical clerkship began learning Janna's story through the family's account and ER notes. He diligently prepared for presenting his new patient on rounds later that day.

When the attending asked Mr. Alstadt the reason for Janna's admission, Mr. Alstadt recalled the story and was poised with several sets of clinical guidelines and algorithms from various sources that he had researched overnight [1,2]. He quoted beautifully from them, and most of them seemed to support admitting Janna for a full sepsis workup.

The attending physician was not convinced. "Really? Who recommends a full sepsis workup for a moderately ill, 2-month-old infant likely to have reliable follow-up with her parents? In my clinical judgment, this patient should have been sent home last night, maybe after taking a blood culture, but definitely without a lumbar puncture. I think medical

school should spend less time teaching you those guidelines and give you more time to really see patients. That's where you learn to practice medicine. Well, she's here now. Let's go see her."

The team walked to Janna's room, where they found an infant whose temperature was now 37.3° C, sleeping pleasantly. Her parents appeared tired, but relieved.

The attending physician glanced at Mr. Alstadt and smiled.

## Suggested Readings

- Harper MB. Update on the management of the febrile infant. *Clinical Pediatric Emergency Medicine*. 2004; 5:5-12.
- Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med*. 2000;36:602-614.

## Commentary 1

by Francis A. Neelon, MD

The case vignette sets the values surrounding evidence-based medicine and the art of medicine in stark contrast to one another, as though educators and students must choose one or the other. I think this false dichotomy might be avoided if we used terms like "evidence-based treatment" or "evidence-based evaluation" instead of "evidence-based medicine," which implies that "evidence" is the be-all and end-all of medical practice rather than a small, albeit important, part. It would also help if we emphasized that what one does with evidence-based information is to apply it with judgment. This is never simple; 2500 years ago, Hippocrates already knew that "experience is fallacious and judgment difficult" [1]. Real science is our only defense against the fallacy of experience, and an open mind and careful attention to the patient, our only hope for achieving good judgment.

The evidence-based protocols now available derive from statistical analysis of large numbers of patients, assembled according to a specific diagnosis and treated in a standardized way. Such analyses rely on the fact that, in at least some ways (for example, in their shared diagnostic label), those people are similar to one another. They share similarities, but they are not identical. Judgment, on the other hand, represents the application of evidence-based guidelines to this individual person or that individual person (my patient). Judgment attempts to deal with and respond to the ways in which even people with the same diagnosis differ from one another. While I steadfastly support the value of properly conducted science in uncovering what is the best thing to do, in general, I am always fearful that any given patient may be part of the fraction of study subjects who did less well than the majority under the evidence-based protocol. So I try to decide whether the characteristics of my patient make it likely that he or she will respond like the study majority, and—even if I decide "yes"—I need to be constantly vigilant for any clues that we should change course, no matter what the evidence-based guidelines say. I am always mindful of the fact that statistics are "what happened to 100 other people"; no matter how good evidence-based treatment may be in the aggregate, it may be very bad in *this* individual. So the commitment of the doctor must be not just to prescribe what is best, but also to stay in contact with (and that means to be *personally* available to) the patient, to be sure that the chosen path was in fact a good one.

## Five Percent Science; 95 Percent Judgment?

I agree that scientific data must inform our decisions. But such decisions account for maybe 5 percent of my daily work. The other 95 percent (and some days it is more) is devoted to convincing patients to actually *do* or continue to do what seems clearly to be the best thing. That is what I would call the Art of Medicine, and it is what consumes most of my time and energy. Let me give you an example. Every day I see patients with obesity and type 2 diabetes. I know that both conditions can (usually) be "cured" by weight loss and exercise. I tell patients but they rarely do either, so I offer them pills and, when these fail, insulin. The questions I ask myself are: do I collude with those patients by agreeing to prescribe medications while they refuse, in word or deed, to do the more important things (lose weight and exercise)? How do I get them to change their lives rather than swallow chemicals, especially when I "know" which is truly best? Should I say "No" as long as they are unwilling to say "Yes" to their part of the bargain? How often do I

really try, no matter how recalcitrant the patient, rather than pulling out the prescription pad to truncate the visit and reap the monetary rewards of increased clinical throughput? Evidence-based evaluation and treatment is just the beginning of clinical work.

I would say this about the vignette itself: I think that much more was going on in the scenario than meets the eye. Why was the unnamed attending physician so unhappy with the decisions that were made? The baby was better; Mr. Alstadt learned a lot; the parents were relieved; the hospital made some money. Is the attending physician a "clinical arrogant," unable or unwilling to learn by watching young people do good things that do not spring directly from his own lips? Many years ago, Eugene Stead reminded us that the "most effective teachers create a shadowy framework on which the student can climb" [2], and Morton Bogdonoff once said within my hearing that a teaching hospital is a teaching hospital "because patients teach students who teach interns who teach residents who teach attending physicians." Clinical instructors need to remember those things. On the other hand, was Mr. Alstadt a bit overconfident, presenting his conclusions with such preening arrogance that the attending physician felt compelled to stake out his own territory? All teachers feel that way at some time, and no one profits from it. So the teaching/learning atmosphere could have been much enhanced, if only both participants could achieve a sense of collegial inquiry into whatever evidence-based recommendations are available, and the exercise of good judgment on behalf of the patient.

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## References

1. Hippocrates, *Aphorisms*. Adams F, trans. Available at <http://classics.mit.edu/Hippocrates/aphorisms.1.i.html> Accessed October 28, 2004.
2. Stead EA Jr. The limitations of teaching. *Pharos*. 1969;32:54-57.  
[Google Scholar](#)

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## Commentary 2

by Robert H. Pantell, MD

The optimal management of fever in young infants has been a hot topic in pediatrics for over 30 years. Physicians have always used clinical judgment in deciding on the best strategy to deal with a patient's problem. Infants, however, cannot tell their own stories, and clinical signs and physical findings are often less reliable than in older babies and children. Furthermore, serious infections may develop and progress more rapidly in young infants. In the 1970s a re-emergence of group B beta streptococcal disease in newborns, as well as late onset group B streptococcal infections in early infancy with accompanying reports of considerable morbidity and mortality, concerned physicians. Reports emerged that clinical judgment was often inaccurate in identifying whether febrile infants had a minor respiratory infection or sepsis [1]. Consequently many academic medical centers developed policies to perform a complete sepsis work-up on all febrile infants. Some institutions limited this policy to infants less than a month old while others included infants as old as 3 months. In addition to obtaining blood for CBC and culture, clinicians were required to obtain urine by catheterization for analysis and culture. Lumbar punctures were required to analyze and culture cerebrospinal fluid. All infants were then placed on appropriate intravenous antibiotics and hospitalized for 2 to 3 days until culture results were known.

These policies were designed to minimize the likelihood that an untreated occult infection in a febrile infant would progress and harm the child. Unfortunately the procedures, antibiotics, and hospital experiences also carry their own potential for harm. The iatrogenic consequences of this policy of hospitalizing febrile infants were highlighted in a 1983 report [2]. Furthermore, all antibiotics have adverse consequences; lumbar punctures have a very small but

documented morbidity and mortality, and hospitals are sources of nosocomial infections and medication errors. Finally, the psychological and financial costs of hospitalizing young infants are considerable.

Despite many published reports advocating for such policies, implementation was far from universal, particularly by practicing pediatricians. Most recommendations came from institutions caring for large populations of poor children living in the inner city and utilizing emergency rooms. Pediatricians wondered how relevant these studies were to their individual populations of patients. Also, one study suggested that if these guidelines were strictly followed, between 5 percent and 10 percent of infants less than 3 months old seen in a community practice would be hospitalized [3].

In the late 1990s, the Pediatric Research in Office Settings (PROS) network of the American Academy of Pediatrics sought to clarify the optimal strategy for managing febrile infants. This nationwide network of more than 1000 clinicians was able to study a broad cross-section of infants with a diverse geographic, economic, and ethnic mix. In PROS' Febrile Infant Study, 573 clinicians recorded their usual practice in caring for 3006 episodes of fever in infants less than 3 months old along with clinical outcomes [4].

This study differed from most previous studies by having infants from community practices. Unlike many patients seen in emergency rooms, these infants/families are often well known by their clinicians. In primary care practice it is also customary to follow such patients closely. In this study most infants had an additional visit and phone follow up. Only about 40 percent of the clinicians followed the published policies. (Note: Although there are common references to fever "guidelines," and many respected clinicians and researchers have published their versions of optimal care, no professional society or governmental group has issued "guidelines" on the management of febrile infants). The PROS study documented 54 cases of bacteremia and 14 cases of bacterial meningitis (5 were simultaneously bacteremic) out of the more than 3000 fever episodes. These were considered the most serious illnesses, ie, those for which a delay in diagnosis and treatment could have serious consequences for infants. Of the 63 infants with these diagnoses, 61 were treated with appropriate antibiotics at the initial visit. The other 2 infants were identified in a timely fashion and treated and had no sequelae. Of interest, had the "guidelines" been followed, 3 cases would have experienced delays in treatment (no statistical difference) but there would have been substantially more infants tested, treated, and hospitalized [4].

What does this all mean and how is it relevant to this case? First, it is important to realize that the PROS clinicians were experienced, with a median age of 45. In other words, to allow a suitable place for clinician judgment may require truly *experienced* clinical judgment. When clinical judgment becomes *experienced* judgment is a difficult question, but this model is clearly not for interns in July, unless they have consulted with an attending physician.

## Who decides?

The second point is to question who actually makes the decision. In this hypothetical case the Kendalls were told that the information was complex and the residents didn't want to confuse them. In fact, almost all parents have to deal with complex information and decisions in their personal and professional lives, and few are as critical as those pertaining to the health of their children. You have their undivided attention! And the information can be presented in a meaningful way to help the parents participate in active decision making. In some situations clinicians should be fairly directive: "Jason looks very ill to us; he is only 2 weeks old and is minimally responsive. We are concerned enough that we plan to do a number of tests, including a spinal tap for which we will need your permission, after which we will start antibiotics and plan to observe him in the hospital until we are certain of the best course." The PROS Febrile Infant Study provides valuable information on the risks of serious disease given various clinical findings. Most of the findings of the PROS study are consistent with the intent of the guidelines, placing the sickest-appearing, youngest, and most febrile infants at highest risk. One of the values of this large study is that it allows clinicians to estimate the absolute risk of various scenarios in addition to the relative risks associated with clinical features. Therefore, another scenario could sound like this: "Even though Suzy is only 5 weeks old, she is very interactive and appears only minimally ill. With a temperature of 38.3 C, we estimate that her risk of serious illness is less than half a percent. While we could go ahead and do some blood tests if you are concerned, we have an option of following her closely by seeing her again in the morning, or sooner if you like. I would like to examine her urine today. If that is okay, you could take her home. Do you have our phone number if you need to call?" This gives the parent the option of asking questions, as well as considering whether they are risk-averse and wish more laboratory

testing given the probabilities presented.

While guidelines certainly have a role in clinical medicine, they should never be viewed as commandments. In some settings—such as busy emergency rooms serving patients with whom patient follow-up is challenging—better adherence to guidelines may be appropriate. Community practitioners caring for patients who can be followed closely can exercise individualized clinical judgment along with information generated from the PROS study and knowledge about the individual family to provide optimal care. The bottom line for this debate was captured by a clinician after poring over much of the data, including risks and odds ratios, from the PROS study (Maureen Shannon, personal communication): "If you want commandments or God, go to church; if you want odds, go to Vegas; if you want good clinical care, go to a good clinician."

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## References

1. Roberts KB. Young, febrile infants: A 30 year odyssey ends where it starts. *JAMA*. 2004; 291:1261-1262.  
[View Article](#) [PubMed](#) [Google Scholar](#)
  2. DeAngelis C, Joffe A, Wilson M, et al. Iatrogenic risks and financial costs of hospitalizing febrile infants. *Am J Dis Child*. 1983;137:1146-1149.  
[View Article](#) [PubMed](#) [Google Scholar](#)
  3. Pantell RH, Naber M, Lamar R, et al. Fever in the first six months of life: risks of underlying serious infection. *Clin Pediatr*. 1980;19:77-82.  
[View Article](#) [PubMed](#) [Google Scholar](#)
  4. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291:1203-1212.  
[View Article](#) [PubMed](#) [Google Scholar](#)
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## Commentary 3

by Timothy Quill, MD

Not being a pediatrician, I may be demonstrating a certain hubris discussing clinical reasoning around a febrile infant where the possibility of meningitis has been raised. I remember certain "rules of thumb" from my training: if you simply *thought* of doing a lumbar puncture (LP) as part of a fever work-up, you must proceed. The implicit message was that meningitis was so dangerous that any possibility, no matter how small, warranted the procedure. Our only choice when we felt an LP was clearly not indicated was to not think of the possibility, or at least not talk about it. Clearly there must be a better way.

The development of algorithms or guidelines has been part of an effort to use best available evidence to counteract some of the irrationalities and irregularities that result when one relies totally on the clinical judgment and inherent biases of individual physicians. These more sophisticated "rules of thumb" usually rely on characteristics of population-based studies as well as on expert opinion to guide physicians to make rational choices more on the basis of available clinical evidence than on individual clinical experience. In many instances, such guidelines have improved the quality of care in areas where the evidence is clear (for example, the use of ACE inhibitors in heart failure [1] and not using antibiotics for uncomplicated sinusitis [2]) and where practice variation has been wide and irrational.

Algorithms and guidelines are well suited to common dilemmas such as the febrile infant [3], where there may be a low probability of a dreaded disease like bacterial meningitis, where there may be clinical markers that increase or decrease the probabilities, and where the consequences of delay in diagnosis and treatment can be lethal. Thus, when one thinks of meningitis in the differential diagnosis of a febrile infant, one must think in terms of thresholds (probability of meningitis). Since the consequences of missing the diagnosis of bacterial meningitis are so profound,

the threshold for treatment must be relatively low. But the threshold cannot be so low that we return to the level of "if you think of meningitis, you must do a lumbar puncture," or so high that we put some infants unnecessarily at risk for the consequences of untreated infection because we're reluctant to intervene. If we say the probability of meningitis in this infant was about 5 percent, then we would do 19 unnecessary LPs for every case of meningitis. Importantly, although the case may appeal to our sentiments with its happy ending, this misses the point. The fact that this baby looks fine the next day does not tell us anything about the appropriateness of the LP and antibiotics in the first place.

Guidelines have been very helpful in standardizing best practices, but they cannot be applied rigidly and unthinkingly. They define standards of care in highly restricted circumstances and force clinicians to justify why they recommend variation, if they choose to do so. Of course, one can also "unbundle" a guideline (ie, by following 1 part of the guideline but choosing not to follow another) in this case by performing an LP without empirically starting antibiotics if the pretest probability is low and the initial cell counts appear negative. Conversely, if the child looked sicker or had an exposure to a known case of meningitis, such that the pretest probability approached 50 percent, empirically starting antibiotics while doing the LP might have been the best course. Thus, the existence of a guideline or algorithm does not preclude the need to exercise clinical judgment. Part of that judgment requires that probabilities of alternate outcomes be estimated based on existing studies in light of clinical experience, and then the reasons for particular actions are clearly explained.

## **Communicate Evidence to Parents**

The area where the physicians in this vignette were most inadequate was not in the decision to do an LP and start empirical antibiotics but in their inability or unwillingness to make every effort to make their thinking transparent to the parents first, and to the medical student second. With all the work that has been done promoting evidence-based decision making, there has been a minimal amount of empirical work discovering how best to communicate about this evidence; this is necessary for making the best possible decisions with patients and families [4]. In this low-probability situation, the parents might have been told about the odds of bacterial meningitis using either lay terms ("small chance") or numbers ("5 percent chance"), and then told that the physicians' recommendation is that empirical treatment be started even though the odds are much higher (95 percent) that there is no such infection.

Most parents would accept such recommendations, but some might want to have further input in this situation based on their values and personal experiences. For example, if one of the parents had had a serious allergic reaction to antibiotics, or held a belief system that precluded the use of Western medicine, he or she might ask some hard questions about risks and benefits of empirical treatment. Physician and family would agree that they all had the infant's best interests in mind, and they would then seek common ground around the best possible treatment rather than entering into a power struggle [5]. Physicians should not shy away from making recommendations when the evidence about the best approach is clear from a medical point of view [6], but they must also learn to explain their recommendations in easily understandable terms. They must listen carefully to, and learn from, patients and families to be sure both parties understand one another. When a child is involved, additional ethical obligations of representing a patient with no actual voice in the discussion are added to the mix. The communication skills needed to conduct this part of an interview are not well taught in medical school, and most clinicians have not been observed or evaluated on their skill level. Therefore, practice variation is probably quite large, further adding to the gap between best evidence and best practice.

In a similar vein, the medical student should not get the message that guidelines in general are useless, just that they need to be interpreted in light of clinical judgment. The attending might ask the students about their view of the odds that the patient had meningitis the evening before when they were engaged in decision making and then discuss the probabilistic thresholds for doing an LP and for starting antibiotics. More sophisticated trainees might then be asked how they would present their recommendations to the parents and how they would engage them as partners. Blindly following published guidelines should be discouraged, but using guidelines as a starting point for clinical decision making is clearly on the right track. "Really seeing patients," as suggested by the attending physician, should be encouraged, but the clinical thinking needs to be quantified, and the potential consequences of action and inaction explored in light of available evidence. Then, making one's thinking transparent with patients, families, colleagues and trainees, and engaging them fully in the process, finally closes the loop of delivering the best possible treatment.

## References

1. Jong P, Demers C, McKelvie RS, et al. Angiotensin receptor blockers in heart failure: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2002;39:463-470.  
[View Article](#) [PubMed](#) [Google Scholar](#)
2. Williams JW Jr, Aguilar C, Cornell J, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev*. 2003(2);CD000243.  
[View Article](#) [PubMed](#) [Google Scholar](#)
3. Harper MB. Update on the management of the febrile infant. *Clinical Pediatric Emergency Medicine*. 2004;5:5-12  
[View Article](#) [Google Scholar](#)
4. Epstein RM, Alper BS, Quill TE. Communicating evidence for participatory decision making. *JAMA*. 2004; 291:2359-2366.  
[View Article](#) [PubMed](#) [Google Scholar](#)
5. Fisher R, Ury W, Patton B. *Getting to Yes: Negotiating Agreement Without Giving In*. Boston: Houghton-Mifflin; 1981.  
[Google Scholar](#)
6. Quill TE, Brody H. Physician recommendations and patient autonomy: finding a balance between physician power and patient choice. *Ann Intern Med*. 1996;125:763-769.  
[View Article](#) [PubMed](#) [Google Scholar](#)

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