

# Pediatrics<sup>in</sup>Review<sup>®</sup>

## **Evidence-based Medicine : Applying Valid Evidence**

Gary M. Onady

*Pediatrics in Review* 2009;30;317

DOI: 10.1542/pir.30-8-317

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pedsinreview.aappublications.org/content/30/8/317>

An erratum has been published regarding this article. Please see the attached page for:

<http://pedsinreview.aappublications.org/http://pedsinreview.aappublications.org/content/30/12/485.full.pdf>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2009 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Evidence-based Medicine: Applying Valid Evidence

Gary M. Onady, MD, PhD\*

**Author Disclosure**  
Dr Onady has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## Introduction

This fifth article in the evidence-based medicine (EBM) series integrates the first three steps of EBM introduced previously (asking an answerable question, searching the literature, critical evaluation of the literature) into a fourth step that applies valid evidence discerned in those steps to medical decision-making. Integration of EBM with medical decision-making constitutes the foundation of what has been termed evidence-based practice (EBP). By definition, EBP is the integration of best research evidence with patient values and clinical circumstances to make clinical decisions. (1) Developing an EBP involves conscientious decision-making based on evidence combined with knowledge of patient characteristics, situations, and preferences, and requires three additional tasks:

- Define the problem
- Identify a rational differential diagnosis
- Develop an action plan

This contribution to the EBM series applies previously introduced components from the EBM tool box to convert a problem presented by a patient into a set of rational diagnoses. Additional tools are used for judicious selection of diagnostic testing that prioritizes the diagnoses effectively. Finally, methodology that allows the choice of a definitive action plan is described so a clear decision point can be reached confidently, once a single working diagnosis is given priority. A case referred by an otolaryngologist for preoperative clearance illustrates these points.

*A 4-year-old girl scheduled for tonsilloadenoidectomy has a history of chronic rhinitis, pharyngitis, and recurrent epistaxis. Family history reveals a grandfather who has type I von Willebrand disease (vWb). Physical examination of the girl reveals multiple bruises in various stages of resolution.*

## Step 1: Define the Problem

The question posed by the surgeon is, “Can you clear this patient for surgery?” The process of defining a problem begins by rephrasing the surgeon’s question into a question whose answer facilitates achievement of the real goal, which is to minimize surgical risk. The best initial problem-defining EBM question becomes, “What is the likelihood that this girl has vWb as the cause of her recurrent epistaxis?”

## Step 2: Identify a Rational Differential Diagnosis

The search term “differential diagnosis” is used to filter the numerous publications that address the topic of “recurrent epistaxis.” A relevant article by Sandoval and associates (2) that presents the data summarized in the Table is found by using this search method. The validity of this article, based on critical evaluation relevant to the patient, is excellent and meets all criteria from the Users’ Guide summarized in a previous article in this series. (3)

This differential diagnosis is refined further by asking, “Do this patient’s family history and physical findings uniquely influence the differential diagnosis before any laboratory testing is done?” A clinical manifestations search leads to a highly relevant article containing a strong validity score written by Nosek-Cenkowska and colleagues. (4) Their data allow the calculation of likelihood ratios (LRs), which

### Abbreviations

**ADP:** adenosine diphosphate  
**EBM:** evidence-based medicine  
**EBP:** evidence-based practice  
**Epi:** epinephrine  
**FD:** factor deficiency  
**LR:** likelihood ratio  
**PFA:** platelet factor analyzer  
**PT:** prothrombin time  
**PTT:** partial thromboplastin time  
**vWb:** von Willebrand disease

\*Department of Pediatrics, Boonshoft School of Medicine, Wright State University, Dayton, Ohio.

Table. **Differential Diagnosis of Epistaxis, All Children**

| Differential Diagnoses        | % of Entire Group | 95% Confidence Intervals |
|-------------------------------|-------------------|--------------------------|
| No coagulopathy               | 67                | 57 to 77                 |
| von Willebrand disease        | 19                | 13 to 26                 |
| Platelet aggregation disorder | 6                 | 3 to 9                   |
| Thrombocytopenia              | 4                 | 2 to 6                   |
| Factor deficiencies           | 4                 | 2 to 6                   |

Data from Sandoval et al. (2)

suggest a nearly 20-fold increased likelihood of this patient having vWb because of her history of recurrent epistaxis (LR=1.5), positive family history (LR=1.8), and multiple bruises (LR=7.2) ( $1.5 \times 1.8 \times 7.2 = 19$ ). LRs were detailed earlier in this series. (3) The accompanying tutorial (Fig. 1) illustrates their application to this case. The 19% chance of having vWb reported in the differential diagnosis article, which pertains to a general pediatric patient population, is increased to 82% based on this specific patient's circumstances, as derived from the Nosek-Cenkowska article (Fig. 1).

### Step 3: Develop an Action Plan

The action plan evolves from additional refinement of the differential diagnosis. The exhaustive consideration of all possible differential diagnoses for a particular clinical problem would result in a "possibilistic" approach that requires the patient to undergo unnecessary testing. (5) The list can be trimmed to a probabilistic priority by finding one leading "working" diagnosis and a limited number of prognostic active alternative conditions that

could result in serious consequences if left undiagnosed and untreated. Rare or less serious pragmatic alternative diagnoses are addressed only if the more probabilistic or prognostic alternative diagnoses become less likely as the action plan unfolds.

The working diagnosis in the illustrative case is vWb (82%); no coagulopathy is the active alternative (8%), with platelet aggregation disorder, thrombocytopenia, and factor deficiencies each representing about 2% of the refined differential diag-

noses, thus becoming pragmatic alternatives at this point in the decision-making process.

The action plan is directed to categorize pretest differential diagnoses to a point where medical decision-making is optimized. Tests having LRs from 1 to 5 only minimally increase the probability of a diagnosis significantly. Test LRs of 5 to 10 are more valuable, and when greater than 10, are extremely valuable at increasing disease probability significantly. Similarly, a negative test LR applied to an active alternative diagnosis has little effect in diminishing disease probability when the ratio is between 0.5 and 1, a moderate effect occurs between 0.5 and 0.2, and a marked effect occurs at less than 0.2. The relationships among a working diagnosis, active alternative diagnoses, pragmatic diagnoses, and the influence of diagnostic testing on the action plan are illustrated in Figure 2.

A literature search for diagnostic testing for this case finds a high validity assessment of platelet aggregation in screening for vWb by Favaloro and associates. (6) These authors compared platelet factor analyzers (PFAs) using adenosine diphosphate- (ADP) and epinephrine- (Epi) coated cartridges for ruling out vWb based on their high sensitivities. Their data provide a +LR=8.2 and -LR=0.26 for PFA:ADP, with a +LR=3.14 and -LR=0.05 for PFA:Epi. The priority set for our case in moving along the action plan is to look for testing that is relevant to the working diagnosis because there is no reason to pursue a test for the active alternative of no coagulopathy and because the remaining pragmatic diagnoses are at such a low probability that testing for these options is impractical.

#### Tutorial: Working with Probability and Likelihood Ratios

Probability/(1-Probability)=odds; from our example,  
 $0.19/(1-0.19)=0.23$

Likelihood ratios, which reflect odds, can be applied directly to pretest odds as follows:

$$0.23_{\text{Pre-test odds}} \times 1.5_{\text{LR Recurrent Epistaxis}} \times 1.8_{\text{LR Family Hx}} \times 7.2_{\text{LR Multiple Bruises}} = 4.5_{\text{Pre-test odds Revised}}$$

Odds/(1+Odds)=Probability; from our example,  
 $4.5/(1+4.5)=0.82$  or 82%

Figure 1. Working with probability and likelihood ratios.

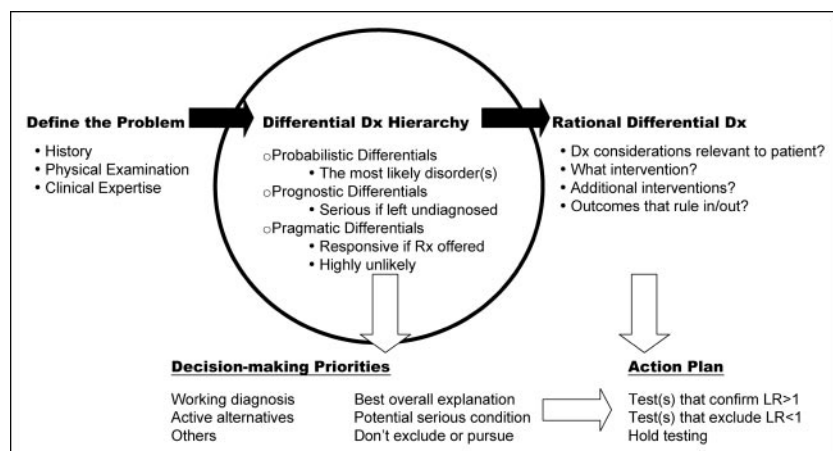


Figure 2. Evidence-based practice approach toward action plan development. Dx=diagnosis, Rx=treatment, LR=likelihood ratio.

At what point is the decision to take action on a working diagnosis met? The goal now is to move to a point where an action threshold (to order a test or recommend treatment) is crossed. Action thresholds vary and depend on disease severity and the benefit or risk (cost) of the intervention. Consider the working diagnosis of the life-threatening disease acute lymphocytic leukemia, in which highly toxic chemotherapy is chosen to induce a remission. The ideal “rule in” threshold must be achieved to beyond a 95% chance of disease because the risk associated with therapy is very high relative to the chance of inducing a remission.

At times, an action plan to “rule out” an active alternative diagnosis takes priority, in which case the goal is to choose testing that, if achieving negative results, would strongly diminish the chance of that disorder being present. The process again depends on the time frame in which a decision must be made and the seriousness of the illness. Ideally, a point at which harm from therapy is higher than risk of the disease itself shifts the action plan back toward prioritizing the working diagnosis. This is the approach used to treat the “febrile infant without a source” with intravenous antibiotic therapy because there is a 10% chance of the severe consequence of sepsis being present until blood cultures are read as negative at 48 hours, at which point this active alternative diagnosis falls to a point well below 5%.

Defining a point at which a positive outcome prevails validates a rational action plan. Ideally, treatment thresholds validate a critical decision-making point. Treatment threshold identifies the point at which the benefit of treatment outweighs the risk of harm (cost) based on the relationship (7):

$$\text{Treatment threshold} = 1 / ([\text{Benefit}/\text{Cost}] + 1)$$

In considering our case, weighing the risk of hemorrhage versus the harm of inducing hyponatremia by recommending preoperative desmopressin, which is a therapy used to prevent bleeding in patients who have vWb, is the final task that must be addressed in this decision. An article by Derkey and colleagues (8) was found by using a prognostic literature search to address this concern. The authors reported a 20% decrease in bleeding in patients treated with desmopressin, with a 25% occurrence of hyponatremia observed in the treatment group. Results using the previously cited equation gives a

$1 / ([0.20/0.25] + 1) = 56\%$  treatment threshold. Therefore, if the probability of vWb is greater than 56%, the benefit of preventing operative hemorrhage outweighs the risk of hyponatremia associated with desmopressin therapy.

Referring back to the diagnostic testing question, the decision as to which test should be ordered now can be determined clearly. Figure 3 provides a graphic and direct comparison of how separate starting points for pretest likelihood of disease are affected by the outcome of positive or negative test results. This figure also places into perspective many aspects of decision-making that otherwise would be based on gestalt. Placing the entire spectrum of action plan components from Figure 2 into a clear scheme for decision-making is the rationale behind the “Gestaltogram” in Figure 3, which maps these results graphically.

The goal mapped out in Figure 3 is to move the working diagnosis across a decision point, represented by the solid treatment threshold line at 56% for both sets of patients. For our patient, who has a positive family history and clinical findings, the starting point is a probability of 82% (represented by the placement of the vertical bar within the spectrum of likelihood). The PFA:Epi test is the only test of value to a patient who has a high likelihood of having vWb. A negative result decreases the vWb posttest probability below the treatment threshold, thereby supporting the choice not to use desmopressin. Note that a negative PFA:ADP test result does not bring the probability of disease below the treatment threshold, resulting in useless testing because desmopressin still would be chosen, whether the test result was positive or negative. There are better tests than PDA:Epi to “rule in” vWb (discussed in a following section), but this test

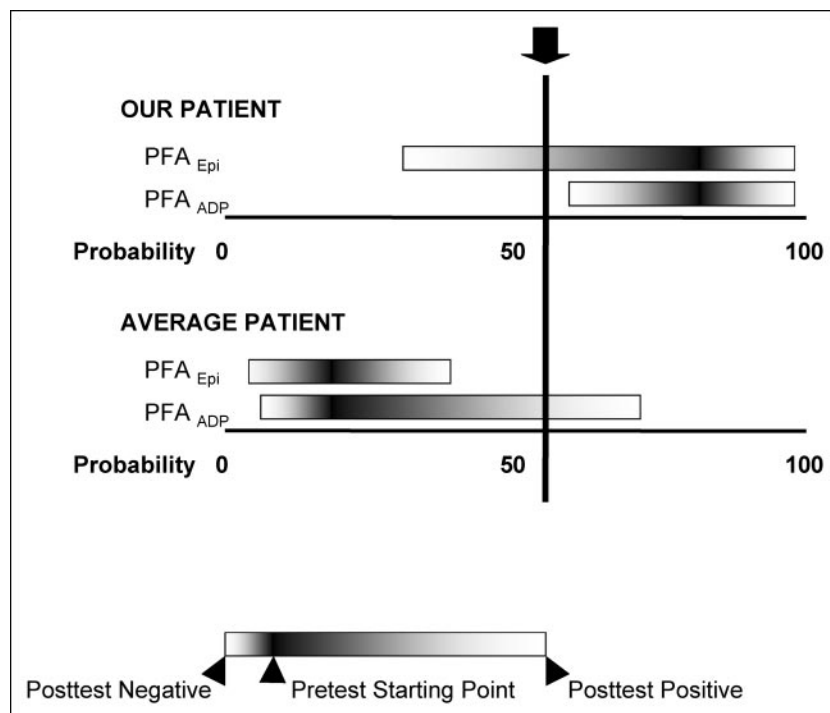


Figure 3. "Gestaltogram" of tests based on risk for von Willebrand disease. PFA=platelet factor analyzer, ADP=adenosine diphosphate, Epi=epinephrine.

has a higher sensitivity than PFA:ADP testing when seeking to diminish the likelihood of disease to a point where risk becomes greater than benefit.

The patient identified in Figure 3 as the "average patient" who does not have a highly suggestive family history or physical findings suggesting a coagulopathy has a 19% starting probability of having vWb. In this situation, a test having a high sensitivity for ruling out a disease is less helpful than a test that is more specific for

2) ruling in a disease, and 3) ruling out a disease.

The clinical goal in using EBM tools for our patient is to optimize a surgical outcome using this EBP application by crossing a decision-making threshold that supports the use of desmopressin. The clear choice is to order PFA:Epi, which was reported positive for this patient, thus definitively establishing the diagnosis of vWb. By following this logical approach, the correct testing was done, and excessive, wasteful testing was avoided.

Having the correct diagnosis leads to therapeutic decisions. The recommendation made to the surgeon is that preoperative desmopressin would benefit this patient, albeit with close serum electrolyte monitoring for the 25% chance of developing hyponatremia. Application of the concept of treatment threshold =  $1/([Benefit/Cost] + 1)$  provides a high level of validation to the axiom of "first do no harm." Physicians may not be able to achieve 100% perfect results, but we do have the ability to minimize harm as much as possible.

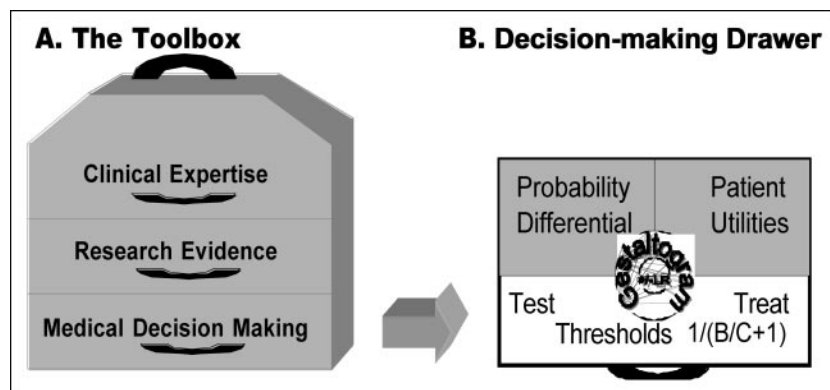


Figure 4. The EBM toolbox and the medical decision-making drawer. LR=likelihood ratio, B=benefit, C=cost (harm).



## A Generalized Evidence-based Practice Plan for Pediatric Patients Who Have Recurrent Epistaxis

The original approach to the case was launched by the pertinent answerable question at the time of presentation, “What is the likelihood that this girl has vWb as the cause of her recurrent epistaxis?” This question was germane to helping the surgeon achieve the best possible clinical outcome, using a prognostic EBP approach. Because an answer was needed quickly, with the patient scheduled for surgery soon, the direct, focused pathway described in the first part of this article was appropriate to obtain the answer in a more timely fashion than could be accomplished by a more comprehensive, time-consuming process.

Going beyond this specific clinical example, the consideration of epistaxis can evolve into a more global question: “What is the expected likelihood of a patient who has recurrent epistaxis being afflicted with a pediatric coagulopathy, as defined by a best EBP diagnostic evaluation designed to rule in or rule out disease?” Answering such a question involves the tasks of defining an appropriate differential diagnosis and formulating an action plan by applying EBM tools. The definitive EBP evaluation illustrated in Figure 5, which focuses on the causes of coagulopathy in a patient presenting with recurrent epistaxis, can be achieved through additional diagnostic testing evidence, as discussed by Acosta and associates (9) and Tosetto and colleagues. (10)

Note that the percentages for disorders in the first horizontal line of the algorithm, which evaluates children who have recurrent epistaxis, are lower than those applicable to a patient who has the additional findings of a family history of vWb and bruises. They are higher than the numbers in the Table, which examines all children who have epistaxis. The element of recurrence introduces an LR of 1.5, which is used to modify the percentages in Figure 5.

Note also that the evaluation depicted in Figure 5 is more comprehensive than the approach taken to answer the surgeon’s inquiry requesting a specific answer in a shorter time. The order of performing the tests listed in the algorithm is determined by considerations of availability, cost, and diagnostic efficacy as well as the desire to exclude more serious conditions. For example, prothrombin time (PT)/partial thromboplastin time (PTT) testing is both sensitive and inexpensive and if yielding negative results, makes the likelihood of a factor deficiency (FD) so low (1%) that the costly specific test for FD is not needed at this point.

Positive PT/PTT testing would result in an enhanced likelihood of an FD, combining information in the Acosta article with that from the original articles on differential diagnosis and clinical manifestations. This change in perspective launches definitive testing, based on the PT/PTT pattern observed. This recommendation provides evidence-based consistency to the diagnostic approach to bleeding disorders recently reported in an article on bleeding disorders. (11)

After testing for FD renders a negative result, focus shifts to vWb because this specific disorder has such a high likelihood of being diagnosed at this stage of the evaluation. If testing reveals a negative von Willebrand panel, the diagnostic focus shifts toward platelet dysfunction. In this evidence-based practice plan, goals are set to rule out or rule in each condition in the differential diagnosis that might apply to patients who appear to have a high likelihood of having a coagulopathy.

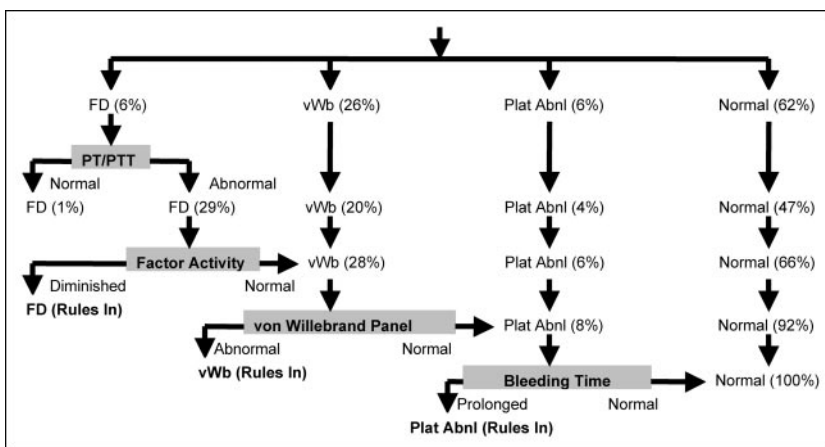


Figure 5. EBP plan for evaluating recurrent epistaxis. Likelihood ratios used in calculating PT/PTT on the differential diagnosis are from Acosta et al (9) and factor activity, vWb, and bleeding time effects on the differential diagnosis are from Tosetto et al (10). Resulting differential diagnoses are proportionally readjusted to equal 100% following calculation of LR effects. FD=factor deficiency, vWb=von Willebrand, Plat Abnl=platelet abnormality, PT=prothrombin time, PTT=activated partial thromboplastin time.

## Conclusions

Would relying on intuition have resulted in the same surgical plan or diagnostic evaluation of a coagulopathy as the EBP approach that was applied to this patient? EBM provides tools to

minimize bias, not just in the critical evaluation of data, but also in how this information is integrated into decision-making components of an EBP. Bias is inherent in using even the best medical evidence. Practice bias has been shown to influence experienced clinical faculty to make optimal medical decisions only 47% of the time. (12)

A highly valid article that focuses on the differential diagnosis provides a starting point for launching a clinical investigation, but inclusion criteria may need to be refined to match a situation unique to an individual patient. Integration of quality evidence from articles focusing on clinical manifestations, as with this patient, provided a more relevant starting point. Clinical bias by the generalist physician not seeing many cases of vWb may interfere with appreciation of a relevant family history and the finding of multiple bruises, which together increase the chances of coagulopathy by fourfold from 19% to 82%. EBM incorporated into an EBP plan shifts a focus of relying heavily on test results toward relying more on our clinical expertise—a refreshing perspective.

This EBP approach also had a significant impact on choosing the most appropriate test for diagnosing this specific patient. Different tests are pertinent to different clinical situations. As demonstrated in Figure 3, PFA: ADP testing, as recommended by the authors, is more applicable to a patient who is at lower risk for having disease, but this specific testing would not have allowed the clinician to make a definitive decision in the unique patient who has a family history of vWb and multiple bruises found on physical examination. This understanding illustrates the fundamental difference between practicing “medicine that is evidence-based,” which applies results coming from a diverse patient population, and the EBM approach, which applies EBP methods to optimize decision-making for an individual patient. Using EBM

tools to construct an EBP takes medical decision-making in new and challenging directions. It has been the intent of this entire series to make this important task easier and more user friendly for the clinician.

## References

1. Shaneyfelt T, Baum KD, Bell D, et al. Instruments for evaluating education in evidence-based practice. *JAMA*. 2006;296:1116–1127
2. Sandoval C, Dong S, Visintainer P, Ozkaynak MF, Jayabose S. Clinical and laboratory features of 178 children with recurrent epistaxis. *J Pediatr Hematol/Oncol*. 2002;24:47–49
3. Raslich MA, Onady GM. Evidence-based medicine: critical evaluation of the literature (critical appraisal tools). *Pediatr Rev*. 2007; 28:132–138
4. Nosek-Cenkowska B, Cheang MS, Pizzi NJ, Isreal ED, Gerrard JM. Bleeding/bruising symptomatology in children with and without bleeding disorders. *Thromb Haemostas*. 1991;65:237–241
5. Richardson WS, Wilson MC, Guyatt GH, Cook DJ, Nishikawa J. Users' guides to the medical literature. XV. How to use an article about disease probability for differential diagnosis. *JAMA*. 1999; 281:1214–1219
6. Favaloro EJ, Kershaw G, Bukuya M, Hertzberg M, Koutts J. Laboratory diagnosis of von Willebrand disorder and monitoring of DDAVP therapy: efficacy of the PFA-100 and vWF:CBA as combined diagnostic strategies. *Haemophilia*. 2001;7:180–189
7. Pauker SG, Kassirer JP. Therapeutic decision-making: a cost-benefit analysis. *N Engl J Med*. 1975;293:229–234
8. Derkay CS, Werner E, Plotnick E. Management of children with vWb undergoing adenotonsillectomy. *Am J Otolaryngol*. 1996;17: 172–177
9. Acosta M, Edwards R, Jaffe EI, Yee DL, Mahoney DH, Teruya J. A practical approach to pediatric patients referred with an abnormal coagulation profile. *Arch Pathol Lab Med*. 2005;129:1011–1016
10. Tosiello A, Rodeghiero F, Castman G, et al. Impact of plasma von Willebrand factor levels in the diagnosis of type 1 vWb: results from a multicenter European study. *J Thromb Haemostas*. 2007; 5:715–721
11. Sharathkumar AA, Pipe SW. Bleeding disorders. *Pediatr Rev*. 2008;29:121–130
12. Hershberger PJ, Part HM, Markert RJ, Cohen SM, Finger WW. Development of a test of cognitive bias in medical decision-making. *Acad Med*. 1994;69:839–842

## Evidence-based Medicine Series

The previous articles in this series on evidence-based medicine can be accessed online:

- Evidence-based Medicine for the Pediatrician (<http://pedsinreview.aappublications.org/cgi/content/full/23/9/318>)
- Asking The Answerable Question (Question Templates as Tools) (<http://pedsinreview.aappublications.org/cgi/content/full/24/8/265>)
- Searching Literature and Databases for Clinical Evidence (Search Tools) (<http://pedsinreview.aappublications.org/cgi/content/full/25/10/358>)
- Critical Appraisal of the Literature (Critical Appraisal Tools) (<http://pedsinreview.aappublications.org/cgi/content/full/28/4/132>)

## Evidence-based Medicine : Applying Valid Evidence

Gary M. Onady

*Pediatrics in Review* 2009;30;317

DOI: 10.1542/pir.30-8-317

### Updated Information & Services

including high resolution figures, can be found at:  
<http://pedsinreview.aappublications.org/content/30/8/317>

### References

This article cites 12 articles, 4 of which you can access for free at:  
<http://pedsinreview.aappublications.org/content/30/8/317#BIBL>

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Evidence-Based Medicine**  
[http://pedsinreview.aappublications.org/cgi/collection/evidence\\_based\\_medicine](http://pedsinreview.aappublications.org/cgi/collection/evidence_based_medicine)  
**Research and Statistics**  
[http://pedsinreview.aappublications.org/cgi/collection/research\\_statistics](http://pedsinreview.aappublications.org/cgi/collection/research_statistics)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
</site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
</site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™





to alkali supplementation, children may develop chronic renal failure. Initial evaluation, management, and follow-up planning routinely involve consultation with a pediatric nephrologist.

### Lessons for the Clinician

- The presence of a nonanion gap metabolic acidosis in the context of

growth failure should alert the clinician to the possibility of net body loss of bicarbonate, either in the GI tract or the renal tubule.

- Although RTA is rare, a clinical history of growth failure in association with analysis of serum electrolytes, urine pH, and urine anion gap can direct the clinician to the appropriate diagnosis.
- Compliance with prescribed alkali

supplementation is important to prevent long-term complications, including renal failure.

(Christina Bourland, MD, UTSW Medical Center, Children's Medical Center of Dallas, Dallas, Tex.)

To view Suggested Reading lists for these cases, visit [pedsinreview.aappublications.org](http://pedsinreview.aappublications.org) and click on Index of Suspicion.

### Clarification

In the article by Onady on evidence-based medicine in the August 2009 issue (*Pediatrics in Review*. 2009;30:317–324), an example is used that involves a hematologic condition. The clinical example presented and the references used in the discussion are meant to illustrate the application principles of evidence-based medicine for an individual patient at a moment of time requiring urgent and sound medical decision-making. That example, using a specific case, was not intended to be part of a clinical guideline. Readers should use the article to understand principles of evidence-based medicine. However, because information has been updated since this case was analyzed, the reader should not apply the material to direct care of individual patients. Clinicians wishing to find more in-depth information on von Willebrand disease are referred to the NCH Guidelines at: [http://www.guideline.gov/summary/summary.aspx?doc\\_id=12275&nbr=006357&string=von+AND+Willebrand+AND+disease](http://www.guideline.gov/summary/summary.aspx?doc_id=12275&nbr=006357&string=von+AND+Willebrand+AND+disease).

In the quiz that follows the article on bronchiolitis in the October issue (*Pediatr Rev*. 2009;30:395), answer D in question 6 reads, in the print edition, “Identify febrile infants >30 days of age who are at low risk for serious bacterial infection and may not need empiric antibiotics.” That answer is correct, and there is a typographical error in the online edition, which reads “<30 days.”