Use of the Likelihood Ratio in the Management of the Young Child With Fever

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The febrile infant is a common clinical problem for the primary health care provider. This paper employs the example of a young infant with fever to describe an important epidemiologic concept that is useful in the interpretation of diagnostic data—the likelihood ratio. The likelihood ratio expresses the odds of a given diagnostic test result occurring in a patient with (as opposed to without) the target disorder.

Likelihood ratios have three properties that are helpful for clinicians: (1) The likelihoods that make up the likelihood ratio are calculated in a manner similar to sensitivity and specificity and therefore show little variation with change in disease prevalence (unlike predictive values, which change dramatically with disease prevalence). (2) Likelihood ratios can be calculated at several levels of a sign, symptom, or laboratory test. (3) Likelihood ratios can be used to shorten the list of diagnostic possibilities because the pretest "odds" × likelihood ratio=post-test "odds" of a disease.

Using likelihood ratios in the practice of primary care medicine should reduce the number of patients with false-positive or false-negative results, sparing some patients needless therapy as well as minimizing the number of patients denied efficacious interventions. Support for likelihood ratios within the primary care medical community will hasten their availability in laboratories of clinical medicine.

The febrile infant is a common, important clinical problem for the primary care health provider. A recent review in *The Journal of Family Practice* summarized a "practical approach" to the febrile infant.[1] The purpose of this paper is to use the example of the febrile infant to describe an important epidemiologic concept that is useful in the interpretation of diagnostic data—the likelihood ratio. Understanding concepts of clinical epidemiology is a fundamental skill "for clinicians who intend to make up their own minds about the soundness of clinical information. Indeed, clinical epidemiology is one of the basic sciences forming the foundation on which modern medicine is practiced."[2]

The likelihood ratio compares proportions of patients with and without the target disorder who have a given level of a diagnostic test result. The given level may mean the presence or absence of a sign, symptom, or any of the levels of a laboratory test result, such as those displayed in Figure 1. "Thus the likelihood ratio expresses the odds that a given diagnostic test result would be expected in a patient with (as opposed to one without) the target disorder."[3]

APPLICATION

Assume that 300 children aged less than 24 months with fever greater than 40°C (104°F) were seen consecu-

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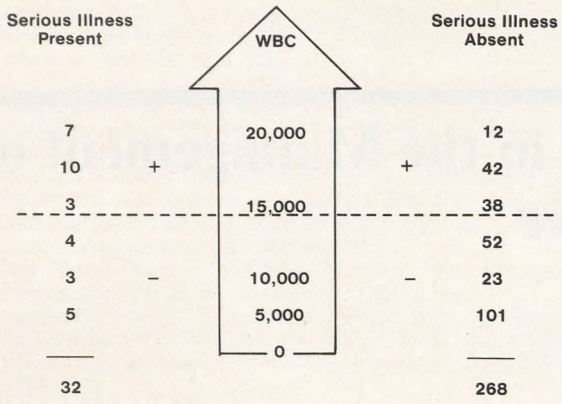

Figure 1. White blood cell count in patients with and without serious illness

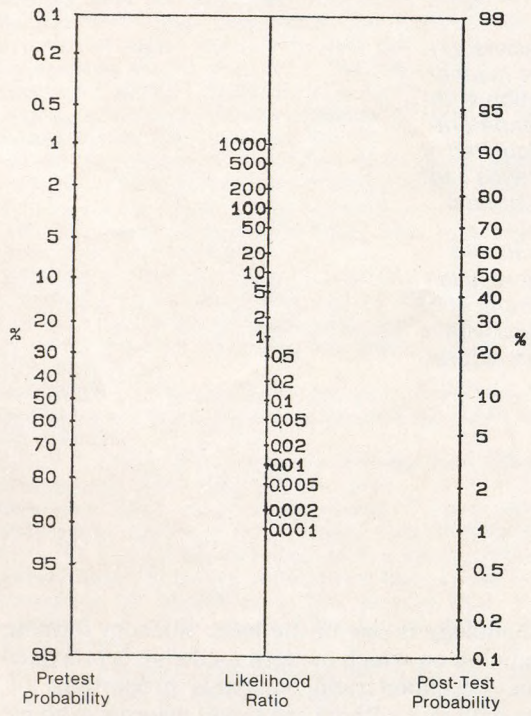

Figure 2. Nomogram for applying likelihood ratios. Figure courtesy of the Department of Clinical Epidemiology and Biostatistics, McMaster Health Center, Hamilton, Ontario

tively in a family medicine clinic. Assume also, as suggested in an earlier paper,[4] that each child was observed for quality of cry, reaction to parent stimulation, state variation (confused, sleepy, alert), color, hydration, and response to social overtures. In addition, a physical examination was performed on each child and a white blood cell count was performed. "Serious illness" was subsequently established in 32 children either by isolation of bacterial pathogens from blood, urine, or cerebrospinal fluid or by abnormalities of electrolytes (hypernatremia or acidosis).

TABLE 1. CONVERSION OF RAW DATA TO 2×2 TABLE

White Blood Cell Count Test Result	Present	Absent	Total
Positive white blood cell level ≥ 15 × $10^3/\mu L$	20 (*a*)	92 (*b*)	112
Negative white blood cell level < 15 × $10^3/\mu L$	12 (*c*)	176 (*d*)	188
	32 (*a* + *c*)	268 (*b* + *d*)	300

Figure 1 shows the white cell count for the 32 patients with serious illness and the 268 patients without serious illness.* In Table 1, these raw data are converted to a two-by-two table. The sensitivity, specificity, and predictive value of a white cell count in a young child with fever can be calculated with ease. Sensitivity is computed by counting the number of patients with the disease and a positive test and dividing that number by the total number of patients with the disease.[5] In this example, 20/32 = 63 percent. Specificity, on the other hand, is computed by counting the number of individuals without the disease who have a negative test and dividing that number by the total number of individuals without the disease.[5] In this example, 176/268 = 66 percent. The sensitivity and specificity of a white cell count for predicting severe illness in this fictitious data set are similar to the sensitivity and specificity actually observed in a sample of 330 febrile children.[6]

Of course, when clinicians order tests, they do not know which patients do or do not have disease. Therefore, they are most interested in the predictive value of a test. The positive predictive value of a test is computed by counting the number of patients with disease and a positive test and dividing that by the number of patients with positive tests in the sample.[7] In this example, 20/112 = 18 percent. The negative predictive value may be computed by counting the number of patients without disease who have a negative test and dividing by the number of patients with negative tests in the sample.[7] In this example, 176/188 = 94 percent.

Though predictive values of a test are more helpful to clinicians than the test's sensitivity and specificity, predictive values also change with disease frequency in a population.[7] In this example, the frequency of serious illness is 32/300 = 10.6 percent, and the positive predictive value of a white cell count with a sensitivity of 63 percent and a specificity of 66 percent is 18 percent. If the sensitivity and specificity remain un-

*Raw data in Figure 1 are fictitious

TABLE 2. HOW LIKELIHOOD RATIOS ARE CALCULATED

White Blood Cell Count Result	Serious Illness: Present — No.	Present — Likelihood	Absent — No.	Absent — Likelihood	Likelihood Ratio
Positive ≥ $15 \times 10^3/\mu L$	20	$\frac{a}{a+c} = \frac{20}{32} = .625$	92	$\frac{b}{b+d} = \frac{92}{268} = .343$	$\frac{.625}{.343} = 1.82$
	a		b		
	c		d		
Negative <$15 \times 10^3/\mu L$	12	$\frac{c}{a+c} = \frac{12}{32} = .375$	176	$\frac{d}{b+d} = \frac{176}{268} = .656$	$\frac{.375}{.656} = .571$
	$a+c$		$b+d$		
	32		268		

TABLE 3. LIKELIHOOD RATIOS FOR SEVERAL LEVELS OF A DIAGNOSTIC TEST RESULT

White Blood Cell Count Result	Serious Illness: Present — No.	Present — Likelihood	Absent — No.	Absent — Likelihood	Likelihood Ratio
≥ $20 \times 10^3/\mu L$	7	7/32 = .219	12	12/268 = .045	.218/.045 = 4.84
15×10^3- $19 \times 10^3/\mu L$	13	13/32 = .406	80	80/268 = .299	.406/.299 = 1.36
10×10^3- $14 \times 10^3/\mu L$	7	7/32 = .218	75	75/268 = .280	.218/.279 = .280
<$10 \times 10^3/\mu L$	5	5/32 = .156	101	101/268 = .377	.156/.377 = .414
	32		268		

changed, but the disease frequency (prevalence) changes from 32/300 to 6/300 = 2.0 percent, the positive predictive value now becomes 4/104 = 4 percent.

Another clinically useful concept in the interpretation of test results is the likelihood ratio.[8,9] Likelihood ratios have three properties that make them extremely helpful to clinicians[3]:

1. The likelihoods that make up the likelihood ratio are calculated vertically, like sensitivity and specificity, and therefore need not change with changes in prevalence of disease.
2. They can be calculated at several levels of a sign, symptom, or laboratory test.
3. They can be used to shorten the list of diagnostic hypotheses because the pretest "odds" of a disease multiplied by the likelihood ratio equals the posttest "odds" of a disease.

For example, Table 2 shows that the likelihood ratio for a positive test result is 1.82. In other words, this level of white cell count elevation is about twice as likely to come from patients with serious illness as it is from those without serious illness. A close look at the proportions that make up the calculation reveals that $a/a+c$ is the test's sensitivity and $b/b+d$ is (1 minus specificity) the complement of the specificity or the false-positive rate. The likelihood ratio for a negative test result is 0.571. Thus, this level of test result is only one half as likely to come from patients with disease as from those without the disease. The first likelihood for a negative test result is 12/32 = 0.375, which is $c/a+c$, the complement of sensitivity, or the false-negative rate. The second one is 176/268 = 0.656 ($d/b+d$), which is the specificity, or the true-negative rate. Therefore, likelihood ratios are derived from test parameters that are stable despite fluctuations in disease prevalence.

The second property is demonstrated in Table 3. If the raw data are stratified into four groups rather than two (ie, positive and negative), then the range of ratios increases 1.82/0.571 = 3.18 in Table 2 to 4.85/0.414 = 11.7 in Table 3. The clinical information from the test result is, therefore, substantially increased.

The third property is a very powerful approach to shortening a list of diagnostic possibilities. If one begins with a clinical estimate of the odds (pretest probability), orders a test, and applies a likelihood ratio for the patient's test result, a new posttest odds (posttest probability) is generated. For example, suppose that a physician knows that a child aged less than 24 months with a fever greater than 40°C has about a 10 percent chance (odds 1:9 or 0.11:1) of serious illness. The physician orders a white cell count, the result of

which is a count of $18.3 \times 10^3/\mu L$. Using Table 3 the likelihood ratio is 1.36. Applying the third property, 0.11:1 × 1.36 = 0.136:1, the posttest probability corresponds to posttest odds divided by posttest odds +1 = 0.136/0.136 + 1 = 11.9 percent. Instead of converting odds to probability, it is convenient to use a nomogram (Figure 2). To use the nomogram for this example, put a straightedge at 10 percent pretest probability and rotate it to a likelihood ratio of 1.36. The straightedge should lie just above the 10 percent posttest probability.

The likelihood ratio can also be used to interpret clinical observations. For example, the data from a sample of febrile young children suggest that the clinical observations described in this example have a sensitivity of 77 percent and a specificity of 88 percent in identifying young children with serious illness.[4] Therefore, the likelihood ratio for serious illness calculated from a positive clinical "test" is 0.77/1 − 0.88 = 0.77/0.12 = 6.4. Using the nomogram with a pretest probability of serious illness at 10 percent in febrile children aged less than 24 months, "positive" clinical observations with a likelihood ratio of 6.4 generate a posttest probability of about 45 percent. The posttest probability of serious illness after observing the child becomes the pretest probability for laboratory tests. Remember that a "positive" white cell count greater than $15 \times 10^3/\mu L$ (Table 2) has a likelihood ratio of 1.82. Using the pretest probability of 45 percent, and employing a straightedge on the nomogram will generate a posttest probability of about 55 percent. However, if one uses Table 3 and a febrile child has a white cell count greater than or equal to $20 \times 10^3/\mu L$, the likelihood ratio becomes 4.95 and, given a pretest probability of 45 percent, the posttest probability of serious illness becomes 75 percent. Note that in this example, clinical observation is a better predictor of serious illness in febrile children (likelihood ratio 6.4) than a white cell count (highest likelihood ratio = 4.95). This example represents a quantitative confirmation of the clinical impression that observation of a febrile patient is more valuable than a laboratory test. The importance of clinical observation is not unique to evaluation of the febrile child. Sackett et al[10] note that three fourths of patients in a general medicine clinic have correct diagnoses at the time of their history and physical examination.

In summary, pretest probability should be estimated when analyzing a diagnostic test result for a patient. The likelihood ratio that corresponds to the first test result can then be applied. The posttest probability, or odds from the first test, becomes the pretest probability, or odds for the next diagnostic test. In addition, the combination of all pertinent symptoms, signs, or laboratory studies that pertain to the target disease may not be independent. Therefore, they may combine to overestimate the final posttest probability of disease.[3] The use of likelihood ratios fits in well with clinical medicine. By making the best use of diagnostic test results (as in Table 3), this strategy allows physicians to place patients at high or low likelihood of disease. This approach should reduce the number of patients with false-positive or false-negative results, thereby sparing some patients needless therapy as well as minimizing the number of patients denied an efficacious intervention.

COMMENT

Although Sackett and his colleagues at McMaster Health Sciences Centre believe that "likelihood ratios will probably become the standard approach for most diagnosticians by 1990,"[10] how should a primary care physician proceed who is slightly ahead of his time (and perhaps his community)? To use likelihood ratios, the physician-diagnostician must have a table of sensitivities and specificities for diagnostic tests and target disorders. Sackett has provided the anlage for such a table in his recent book.[10] In addition, the physician-diagnostician should keep a nomogram handy and begin to think carefully about the pretest probability of disease in a given patient, based on his or her clinical experience and the medical literature. Finally, the physician-diagnostician should request both a laboratory test result and the test's likelihood ratio for a target disorder. The evolution of likelihood ratios from interesting concept to "standard approach" may well be accelerated with support from primary care physicians.

References

1. McCutcheon ML: The febrile infant. J Fam Pract 1985; 20:584-588
2. Fletcher RH, Fletcher SW, Wagner EH: Clinical Epidemiology—The Essentials. Baltimore, Williams & Wilkins, 1982, p 3
3. McMaster University, Department of Clinical Epidemiology and Biostatistics: Interpretation of diagnostic data: How to do it with simple math. Can Med Assoc J 1982; 129:22-29
4. McCarthy PL, Sharpe MR, Speisel S, et al: Observation scales to identify serious illness in febrile children. Pediatrics 1982; 70:802-809
5. Lilienfeld AM: Foundation of Epidemiology. New York, Oxford University Press, 1980, p 151
6. McCarthy PL, Jekel JF, Dolan TF: Temperature ≥ 40° in children less than 24 months of age: A prospective study. Pediatrics 1977; 59:663
7. Barker DJP, Rose G: Epidemiology in medical practice. New York, Churchill Livingston, 1979, p 121
8. Katz MA: Probability of graph describing the predictive value of a highly sensitive diagnostic test. N Engl J Med 1975; 291:1115-1116
9. Fagan PJ: Nomogram for Bayes' theorem. N Engl J Med 1975; 293:257
10. Sackett DL, Haynes RB, Tugwell P: The clinical examination. In Clinical Epidemiology: A Basic Science for Clinical Medicine. Boston and Toronto, Little, Brown, 1985, pp 17, 66, 74-75