BENDING THE VALUE CURVE

Right Test, Wrong Patient: Biomarkers and Value

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A 2-year-old girl with Pierre Robin sequence, a gastric tube, and a tracheostomy and ventilator was admitted to the hospital medicine service. She had presented with a dislodged gastric tube, and on presentation she was lethargic, mildly febrile, and tachycardic, with normal blood pressure for age and oxygen saturations of 95% to 100% on her home ventilator settings. Her laboratory tests in the emergency department were notable for a glucose of 36 mg/dL, a normal C-reactive protein (CRP) and white blood cell count, and a procalcitonin, a commonly ordered biomarker, of 28 ng/mL.1 She was given a dextrose bolus, and her lethargy resolved. She also received a dose of ceftriaxone and was admitted for observation because a procalcitonin level of 28 ng/mL, in our clinical laboratory, is interpreted as being highly suggestive of sepsis. At the time we met her on rounds the morning after admission, her blood cultures had been negative for >24 hours, and she had a reassuring examination and vital signs. Despite the reassurance offered by her clinical appearance, our team was unable to reconcile her laboratory findings and elected to continue observation in the hospital for 48 hours. Given that ∼90% of positive blood cultures become positive in the first 24 hours,2,3 this child was probably safe for discharge. However, we elected to observe her for an additional night; the elevated procalcitonin was concerning, and we did not feel comfortable discharging her from the hospital. The patient stayed for an additional day, received an additional dose of ceftriaxone, and was discharged from the hospital the next morning.

The care delivered to this patient was not unsafe, and she did well. However, the value of care was almost certainly suboptimal. Her parents both missed an extra day of work and suffered the inconvenience of spending an additional night in the hospital. Furthermore, there was the expense of an additional night in the hospital, including expenses related to her ventilator requirement, physician fees, respiratory therapist fees, and the cost of antibiotics. Thoughtful interpretation of diagnostic tests could have improved the value of care for this child.

Procalcitonin is one of many biomarkers used in medicine. In addition to the large number of biomarkers, there is also great heterogeneity in the definition of what constitutes a biomarker; therefore, the National Institutes of Health developed standard definitions and groupings. They define a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of a normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”4 Biomarkers are categorized by their intended use into 4 groups: diagnosis of disease, disease prognosis, disease staging or severity, and response to intervention.4 In the field of pediatrics, procalcitonin is most often used as a marker of bacterial infection in children presenting with fever without a source. Procalcitonin has been applied to the pediatric population and shown to be elevated in patients with bacterial infections and typically not elevated in those with viral infections.5 Multiple studies have examined the utility of
procalcitonin as a marker of bacterial infection in children presenting to the emergency department with fever without a source with similar results. For example, a recent meta-analysis reported a positive likelihood ratio of 3.6 to 13.7 for the presence of bacterial infection when procalcitonin is $\geq 2.0$ ng/mL and a negative likelihood ratio of 0.54 to 0.58 for procalcitonin $< 2.0$ ng/mL. Newer studies have compared procalcitonin with other markers of bacterial infection (eg, CRP and white blood cell count). However, the authors did note that procalcitonin and CRP performed similarly. Another meta-analysis focusing on children 7 days to 36 months of age who presented to the emergency department with a fever found that at a level of 0.5 ng/mL, procalcitonin had a positive likelihood ratio of 2.69, compared with 3.10 for CRP and 2.11 for leukocytosis in detecting severe bacterial infection. Indeed, all these studies demonstrate the utility of procalcitonin in identifying children with a bacterial process. However, procalcitonin is a screening test most commonly used to identify children at risk for bacterial infection or sepsis. Because the outcome (sepsis) can be fatal, researchers chose a low value of the cutoff for a positive test, thereby increasing its sensitivity at the expense of specificity. In other words, it limits the number of false negatives (ie, patients with sepsis whose procalcitonin is negative), but at the same time it increases the number of false positives (ie, patients with a positive test who do not have a serious bacterial infection, such as our patient).

Implicit in medical decision-making is consideration of potential outcomes. When clinicians are deciding to order a test, the concepts of pretest probability, likelihood ratios, and posttest probability can assist them. Pretest probability is formed through integration of history, physical examination, and any other laboratory results available, and it helps the clinician determine the probability that the patient has the diagnosis in question. The likelihood ratio helps the clinician determine how the result of the test affects the probability of disease: A high positive likelihood ratio increases the probability of correctly diagnosing the patient with the disease, known as the posttest probability. For example, the pretest probability of sepsis in a specific cohort of pediatric ICU patients who met systemic inflammatory response syndrome criteria was 39%. The positive likelihood ratio in this study for a procalcitonin level $\geq 2.5$ ng/mL was 2.62. Therefore, when a patient who presented with systemic inflammatory response syndrome had a procalcitonin level $\geq 2.5$ ng/mL, the posttest probability of sepsis modestly increased to 60%. A better understanding of posttest probability and the strengths and limitations of the test will drive better diagnostic test ordering and, perhaps most important for hospitalists, improved understanding of the particular perils of abnormal results from a test that probably should not have been ordered.

When a clinician is considering a procalcitonin test, it can be difficult to accurately determine the patient's pretest probability of sepsis. Several clinical prediction rules have been developed in an attempt to identify patients at high risk of serious infection. A recent review examining several clinical prediction rules in a high-prevalence population, such as an emergency department, found high variability in sensitivities for specific rules and concluded that no single prediction rule was particularly valuable in this setting.

Another review found that the clinical symptoms with the highest odds ratios for serious bacterial infection in pediatric patients presenting to the emergency department include decreased level of consciousness, seizures, cyanosis, tachypnea, decreased capillary refill, parental concern, and clinician concern. The patient in our case presented with lethargy and parental concern. However, her mental status rapidly improved with the administration of glucose, after which she no longer exhibited any clinical signs concerning for sepsis. The lack of a validated, widely accepted way to predict the risk of sepsis in the pediatric population makes determining pretest probability difficult. Although not quantifiable, our patient’s pretest probability of sepsis was low. If her pretest probability of sepsis was estimated at 1%, she would have a pretest odds of sepsis of 1.99. Multiplying those odds by a positive likelihood ratio of 8 for a procalcitonin $> 2.5$ ng/mL (chosen because it is in the middle of the range of likelihood ratios of 3.6–13.7, reported in the aforementioned meta-analysis) gives her a posttest odds ratio of 8.99 and a posttest probability of 7.5%. This modest increase in her probability of sepsis, from 1% to 7.5%, illustrates the limited utility of this test in a patient with low pretest probability of sepsis. Careful consideration should be given to ordering a test of unclear benefit when faced with a patient with a low pretest probability of the diagnosis in question.

With our patient there were several chances to intervene to improve the value of care. The initial choice to order the procalcitonin test in this patient with few risk factors for a serious bacterial infection, a story inconsistent with sepsis, and a clinical presentation probably explained by hypoglycemia was the initial choice that set off a cascade of events. However, continuing to place preferential emphasis on a single laboratory value rather than her clinical picture was the true driver behind the lower value of care delivered to this patient. By better using biomarkers for their intended purpose on appropriately selected children, we will continue to improve the value of care delivered to our patients.

REFERENCES


