Assessing the Febrile Child for Serious Infection: A Step Closer to Meaningful Rapid Results

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All pediatricians have experienced the difficult decision about whether a young infant has a life-threatening infection that requires hospitalization or has a self-limited viral disease that can safely be managed at home. As our appreciation of the negative aspects of antibiotic overuse (both to society and individuals) has matured, these situations have become more rather than less frequent. The almost dizzying development of sophisticated diagnostic modalities over the past 10 to 20 years has, in at least some situations, outpaced our ability to know how to use the test results. No single test has proven adept at accurately distinguishing the child with a life-threatening infection from the child who will get better on his or her own. Into this terrain, Srugo et al[1] increase the number of tools in our toolbox and potentially move us substantially closer to that Holy Grail of accurately determining which child truly is at risk for having a serious bacterial infection.

To fully scrutinize the results of this large, international study, we must first discuss how we assess the utility of diagnostic tests. The sensitivity of a test is how often a test result is abnormal if a serious infection is present, whereas the positive predictive value is how often an infection is present when the test result is abnormal. The positive likelihood ratio is the degree to which an abnormal test result increases the pretest probability of disease. In comparison, specificity is how often a test result is normal if a serious infection is absent, the negative predictive value is how often an infection is absent with a normal test result, and the negative likelihood ratio is the degree to which a normal test result decreases the pretest probability of disease. Whereas predictive values will vary with the prevalence of disease, likelihood ratios relate only to the sensitivity and specificity of the test itself.[2] Likelihood ratios range from 0 to infinity. Values between 0 and 1 suggest that the disease is not present, and the closer to 0 the value is (eg, <0.1), the lower the probability that the disease is present. In contrast, likelihood ratios >1 suggest the disease is present, and the higher the value is (eg, >10), the higher the probability that the disease is present.[3]

The ImmunoXpert assay (MeMed Diagnostics, Ltd, Tirat Carmel, Israel) assessed in the Srugo et al study[1] generates a likelihood score for viral versus bacterial infection that incorporates assessment of tumor necrosis factor–related apoptosis-inducing ligand, interferon γ-induced protein-10, and C-reactive protein (CRP). The first 2 proteins are more elevated in viral infections, whereas CRP is more elevated in bacterial infections. In comparing this novel assay with the standard laboratory assessments of white blood cell (WBC) counts, absolute neutrophil counts, CRP, and procalcitonin (PCT), the ImmunoXpert assay had superior sensitivity compared with WBC, absolute neutrophil counts, and PCT,

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and superior specificity compared with WBC, CRP, and PCT. Most impressively, the assay's positive likelihood ratio approached 10, and the negative likelihood ratio was 0.07. This suggests that the test results may be able to be used meaningfully in the management of patients to a degree that currently does not exist.

Before we get to that point, however, a number of confirmatory investigations are required. All published studies in which researchers have assessed the ImmunoXpert assay have used specimens that were frozen at −80°C.[1,4–6] Researchers of future studies should use prospective trial designs to determine the performance characteristics of the test in a more real-world manner, including the use of refrigerated specimens. As the authors note,[1] the assay also needs to be assessed in infants <3 months of age because this is a population in which tremendous need exists for improved diagnostics that can drive decision-making in an evidence-based fashion. Immunocompromised children also have a large unmet medical need for improved diagnostics that can reliably distinguish bacterial from viral infections. If the assay is validated in these future studies, performance of randomized trial designs that assess how knowledge of the assay result impacts clinical care should be considered, as has been done with influenza testing.[7]

The work of Srugo et al[1] substantially advances the opportunity to one day be able to more accurately assess patients for risk of life-threatening bacterial infections, saving them from unnecessary hospitalization and antibiotic exposure. By focusing on the initial host response to infection, these investigators add to the rapidly expanding field of molecular diagnostics, in which pathogens are increasingly being detected in clinical specimens but the significance of those detections can be questioned because of false-positive results, copathogens, or simple colonization.[8] Their work also enhances exciting discoveries of patterns of host RNA expression that vary by type of infection.[9–11] Taken together, these advancements bode well for the future of diagnostic assessments of ill children in years to come.

ABBREVIATIONS

CRP: C-reactive protein
PCT: procalcitonin
WBC: white blood cell

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