BENDING THE VALUE CURVE

The Power and Peril of Panels

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A 4-month-old term boy presented to the emergency center with 1 day of fever and 4 episodes of new-onset upper-extremity tonic-clonic movements. Each episode lasted <1 minute, and the infant quickly returned to his neurologic baseline after every occurrence. Results from a complete metabolic panel, complete blood count, and urinalysis were unremarkable. The infant was admitted for continuous video EEG monitoring and to evaluate for more serious infectious etiologies of his symptoms. On hospital-day 1, he had 2 seizures with confirmed epileptiform discharges in the right frontal region. He remained hemodynamically stable, but because of persistent fever and declining level of alertness, a blood culture and cerebrospinal fluid (CSF) studies were obtained. CSF analysis revealed 0 white blood cells, 186 750 red blood cells, a glucose level of 58 mg/dL, and a protein level of 188 mg/dL. Empirical ceftriaxone and acyclovir were administered given the concern for possible bacterial or herpes simplex virus (HSV) infections. HSV nucleic acid amplification testing (NAAT) and bacterial culture results of the CSF were negative. A meningitis-encephalitis (M-E) panel result was positive for human herpesvirus-6 (HHV-6).

On hospital-day 2, ceftriaxone and acyclovir were discontinued. After consultation with the infectious diseases service, ganciclovir was initiated for treatment of presumed HHV-6 encephalitis causing the patient's neurologic symptoms. The following day, the child defervesced, developed an exanthem consistent with roseola, and returned to his neurologic baseline. The rapid improvement may have been unrelated to antiviral therapy. However, uncertainty prompted the medical teams to continue hospitalization until previous authorization for the medication was obtained from the insurance company. The infant was ultimately discharged on hospital-day 5 to complete a 10-day course of antiviral therapy.

FINDING THE VALUE IN THE DIAGNOSIS AND TREATMENT OF HHV-6 ENCEPHALITIS

HHV-6 is one of the most common infections affecting children; 70% to 90% of children are infected by 2 years of age.[1] Most children have a self-limited infection, presenting with fever with or without exanthem subitum, but severe clinical presentations do occur. Febrile seizures are the primary clinical presentation in 8% to 20% of children with HHV-6 infection.[2] HHV-6 is also associated with M-E, although the most severe cases generally occur in immunocompromised patients.[3,4] Nonetheless, M-E caused by HHV-6 has been linked to visual impairment, speech disturbances, and persistent hemi- or quadriplegia, even in previously healthy individuals.[5–8]

There is a limited body of evidence in which the use of ganciclovir in primary infections and reactivation of latent virus in immunocompromised hosts is supported.[9] In hematopoietic stem cell transplant recipients, HHV-6 encephalitis treatment was associated with reductions in both long-term sequelae and early death.[4,10,11] The evidence is less clear in immunocompetent individuals. In case reports, authors describe successful treatment of HHV-6 M-E in children and adults.[12–15] However, these individuals had severe presentations, including respiratory

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failure, status epilepticus, and/or abnormal brain imaging, none of which our patient exhibited. The benefit in children with HHV-6 encephalitis that are hemodynamically stable such as ours is uncertain. Moreover, the risks of treatment with ganciclovir, including gastrointestinal irritation and bone marrow suppression, and the associated costs of the medication may outweigh any potential benefit.

THE POWER OF PANELS

Multiplex polymerase chain reaction panels provide a quick and relatively sensitive and specific means for detecting known pathogens.[16] NAAT-based respiratory virus panels can be used to aid in risk stratification because well-appearing febrile infants with positive respiratory viral panel test results have a decreased risk of serious bacterial infections compared with infants with negative test results.[17,18] Although a single positive test result does not necessarily confer a consistent reduction in risk for any 1 type of serious bacterial infection,[19,20] and asymptomatic infants and children frequently test positive for rhinovirus or enterovirus,[21,22] risk stratification still has potential to be used to reduce durations of unnecessary antibiotics and shorten hospital stays.[23,24]

The commercially available CSF M-E panel used at many institutions can be used to detect 14 different pathogens associated with M-E in ~1 hour once the sample is processed (Table 1). In comparison, the mean time to positivity for CSF cultures obtained from febrile infants ≤90 days of age is nearly 29 hours.[25] A retrospective comparison of the M-E panel to both conventional bacterial culture and pathogen-specific NAATs revealed a decreased time to diagnosis by over 10 hours.[26] Potential benefits include earlier discontinuation of unnecessary antimicrobial therapy and earlier targeting of empirical therapies. Additionally, CSF testing positive for pathogens such as enterovirus has been shown to safely decrease an infant's length of hospitalization.[27] In adult and pediatric retrospective cost analyses, it is suggested that the M-E panel may be more cost-effective than current diagnostic standards[28,29]; however, these cost benefits have not been validated in prospective studies.

TABLE 1 Pathogens Detected on Commercially Available M-E Panel

Bacteria
E. coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae
Viruses
Cytomegalovirus
Enterovirus
HSV-1
HSV-2
HHV-6
Human parechovirus
Varicella zoster virus
Yeast
Cryptococcus neoformans or *gattii*

Adapted from FILMARRAY M-E Panel, BioMèrieux, Marcy-l'Ètoile, France. Available at: https://www.biomerieux-diagnostics.com/filmarray-meningitis-encephalitis-me-panel. Accessed September 6, 2018. HSV-1, herpes simplex virus 1; HSV-2, herpes simplex virus 2; HHV-6, human herpesvirus-6.

THE PERIL OF PANELS

Despite the benefits of diagnostic panels, there are clear potential pitfalls with these powerful clinical tools. For instance, the limitations of a test sensitivity that only approaches 100% may not be considered when interpreting the test result, which could result in missed serious infections. In a clinical setting, the sensitivities for each specific organism on the M-E panel range from ~86% to 100%.[30] Although sensitive, a negative test result does not exclude the possibility that a pathogen contained on the panel is the causative agent in children with M-E. For example, the herpes simplex 1 (HSV-1) test result on the M-E panel was falsely negative on 2 samples with positive standard HSV-1 NAAT results obtained from a cohort of 67 children. Both children exhibited a clinical presentation concerning for meningitis and required treatment with acyclovir.[31] Although researchers in a more recent study of 251 pediatric patients found no such discordance with HSV testing,[32] these varied results can be used to highlight the need for additional verification of the M-E panel as a clinical tool before universal implementation.

The clinician must also know which tests are contained within the panel to avoid duplicate testing and determine which items are relevant to the individual patient. Although the M-E panel was designed to identify the most common causes of meningitis, not all tests included are clinically relevant for all populations. Pathogens more commonly found in pediatric populations such as *Staphylococcus aureus*, *Enterococcus* spp., *Klebsiella* spp., and *Salmonella* spp. are not part of this panel, limiting the test's negative predictive value in pediatric medicine.[24] In comparison with pathogens such as *Escherichia coli* and HSV, testing for HHV-6 has less value to the general pediatric population given the paucity of data guiding the clinical management of this infection. Furthermore, HHV-6 lies latent within monocytes and other cells,[3] raising the concern that the presence of virus DNA may not always be indicative of an acute infection and could lead to treatment with antiviral therapy that may not be necessary.[33] The presence of HHV-6 in our infant with a declining level of alertness influenced our decision to treat with ganciclovir. It is not possible to know if the rapid resolution of the infant's symptoms was attributable to this intervention. The frequency at which clinicians could face such clinical dilemmas involving panel-based testing is not negligible; HHV-6 has been detected in the CSF at the same relative frequency (3.8%; 10 out of 251) as enterovirus (3.8%; 10 out of 251) by using the M-E panel.[32]

WHERE DO WE GO FROM HERE?

We anticipate that as laboratory technology continues to evolve, many of the infections that were previously unidentified and self-resolving, such as HHV-6 in the immunocompetent host, have the potential to become management dilemmas for clinicians. However, without clear evidence of a need for or benefit from treatment as well as a risk of adverse reactions to antiviral therapies, the value of this component of the M-E panel remains

unclear for immunocompetent patients. Identifying a cause for a patient's symptoms could be intellectually satisfying and helpful to patients, families, and clinicians, but important questions remain. Although HHV-6 M-E can be treated, should it be? Which children with positive HHV-6 test results should receive treatment? And at what cost? In addition to the direct cost of the M-E panel, the test result led to downstream costs of treatment and longer hospital stay that were of uncertain benefit to the patient. We anticipate that as panels such as the M-E panel become more widely available and routinely used, so will further research in which these important questions will be addressed. Until then, the potential for panels to improve the value of care provided must be knowingly balanced with the unintended consequences of a positive result, including prolonged hospitalization, medication side effects, and off-label use of treatments. To optimize value in the face of evolving diagnostic technology and uncertain risks and benefits, we recommend physicians learn the contents and test characteristics of the available panels, consider each component's relevance for the individual patient, and consider more precise testing when appropriate. Additional approaches such as clinical decision support by using result interpretation provided by clinical laboratories have been suggested[33]; however, additional studies on the use of these approaches are necessary. One final and potentially provocative solution may be to suppress panel results with limited evidence for a particular population unless specifically requested by a clinician. Regardless of the solution, as panels become more powerful, so too must a clinician's abilities to react appropriately to the results, expected or not.

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