Challenges in the Care of Young Infants With Suspected Neonatal Herpes Simplex Virus

As pediatric hospitalists, we often care for neonates and young infants <2 months of age that are admitted to the hospital because of concern for serious infection. Although there are certain clinical signs and symptoms that raise our concern for neonatal herpes simplex virus (HSV; eg, seizures, vesicular rash, critical illness), there is considerable variability in the management of this population when these provocative symptoms are absent. Should we test for HSV in all well-appearing newborns with fever? Or should there be an age cutoff below which all newborns are tested? If we perform testing, should we always start acyclovir? Should we obtain viral studies of mucosal surfaces routinely or only when we have a high level of suspicion? What role should HSV PCR from suspected HSV lesions of the skin, eye or mouth play, as opposed to viral culture? Under what circumstances is it safe to discontinue acyclovir after the CSF HSV PCR is negative?

Neonatal HSV is rare, with only ∼1500 cases in the United States each year; yet the consequences of delayed treatment are significant. There is little controversy concerning the initiation of HSV testing for infants with clinical signs and symptoms suggestive of HSV. Empiric treatment with high-dose intravenous acyclovir is also not controversial because high-dose acyclovir has been the standard treatment for more than a decade and has a low side-effect profile relative to the risk of untreated HSV infection. However, for infants without clinical signs of HSV, the decision to include empiric testing and treatment is less clear. Although a maternal history of fever and primary HSV infection are associated with neonatal HSV, the absence of maternal history of known HSV is not helpful in predicting which infants should be evaluated for HSV infection. Given that many of these infants will otherwise be admitted and started on empiric treatment of bacterial infection, what is the downside of adding on HSV testing and initiating acyclovir?

Despite many advances in the diagnosis and treatment of neonatal HSV, considerable controversy still exists regarding which neonates and infants require testing and empiric acyclovir. Some experts have recommended that neonates only be tested and empirically treated if they have “HSV-specific” signs and symptoms, such as seizures, vesicles, sepsis-like illness, and/or cerebrospinal fluid pleocytosis. Sarah Long et al have taken a somewhat different approach by performing HSV testing and providing empiric acyclovir to all neonates whose symptoms started at ≤21 days of age. Supporting this recommendation with a review of neonatal HSV cases in their facility, the authors found that 16 of their 32 cases (50%) of neonatal HSV presented with nonspecific complaints (eg, fever alone, without seizures, or skin, eyes, and mouth [SEM] disease). Of these 16 patients who presented with nonspecific complaints, 15 (94%) developed symptoms ≤21
days of age. In another study by Kotzbauer et al, the authors focused on the presentation of neonates with disseminated HSV. They found that all patients presented at ≤14 days of age, with 2 of these patients presenting with fever alone. Following either path has pitfalls, with the possibility of delayed recognition of nonspecific cases on the one hand and the risk of overtreatment and higher costs on the other. Thus, there is no clearly optimal framework for the immediate approach to the infant without specific signs or symptoms of HSV who might, nevertheless, have HSV infection.

It is certainly worthwhile to explore the downsides of routinely adding on viral cultures and HSV PCR testing, along with empiric acyclovir. Shah et al have shown that adding a CSF HSV PCR to the evaluation of a neonate increases the length of stay, thus increasing cost and the risk of nosocomial infection. The authors found that addition of the CSF HSV PCR increased the length of stay by 39% in infants 29 to 56 days of age, with an overall cost increase of 41%. Not surprisingly, the authors also found that a prolonged HSV PCR turn-around time increased length of stay. It is notable that this study was conducted in the absence of a selective protocol that may have eliminated costs through reduced provider variability, and to date we are not aware of published reports of cost and length of stay outcomes in hospitals with a selective diagnostic protocol. The fact that HSV PCR turn-around time varies from hospital to hospital makes it likely that hospitals that send out their HSV testing have a significantly longer wait than hospitals that have in-house HSV testing. The consequences of this may affect a provider’s decision to test and empirically treat for neonatal HSV.

After HSV testing and treatment is initiated, many clinicians are understandably reluctant to discontinue acyclovir until HSV testing is resulted. Hospitals that have access to HSV PCRs that are resulted in ≤24 hours may have a lower bar to test for HSV because this testing will unlikely result in a delayed discharge. Hence, the disparate conditions under which diagnostic decisions are made can have significant impact on practice at any given hospital and likely contributes heavily to the variability in practices across the country.

To further complicate the situation, HSV testing is evolving. The 2012 Red Book recommends that all patients evaluated for neonatal HSV have viral cultures of mucosal surfaces and suspected SEM lesions. In regard to neonatal HSV, clinicians are more frequently using HSV PCR to identify virus in skin lesions and on mucosal surfaces. Insufficient data are available to know the sensitivity and specificity of these tests or to compare them to time-proven technologies such as viral culture. Nevertheless, many hospitals are moving away from viral culture in favor of PCR-based testing. Although the 2012 Red Book still recommends HSV surface viral cultures when HSV is suspected, following this recommendation can be problematic because ≥5 days may be required before results are finalized. So even if your institution subscribes to specific indications for testing, the exact tests available to you and how to best interpret them can be challenging.

Another case in point: the HSV blood PCR is frequently positive in neonates with disseminated disease, with Kotzbauer et al showing that all infants with disseminated HSV that were tested with a blood HSV PCR were positive. The blood PCR is also sometimes positive in infants with isolated SEM and central nervous system disease and may be the first or only HSV test to become positive. The availability of this test, with the more frequent identification of viremia across the spectrum of neonatal HSV infection, serves to create additional questions about duration of therapy and prognosis. Although it may simply be that viremia is common and not indicative of disease severity, it is also possible that neonates with HSV viremia are at high risk of the end-organ effects of disseminated HSV. It would not be surprising to find that some providers are lengthening treatment of SEM disease when the blood PCR is positive, given the newness and uncertain prognostic value of the test.

The 2012 Red Book recommends that all infants tested for neonatal HSV should have blood measurement of alanine aminotransferase (ALT). Elevation of ALT should prompt clinicians to consider disseminated HSV disease because it may indicate hepatocellular injury secondary to disseminated disease. Kotzbauer et al found that 15 of 22 patients with disseminated HSV disease had an elevated ALT and 18 of 21 had an elevated aspartate transaminase. Although the authors indicate that most of the reported laboratory values reflect tests obtained in the first 24 hours of admission, we do not know what percentage of patients had elevated transaminase values on presentation. It is possible that neonates tested early in their illness course with disseminated HSV will not have elevated transaminase levels. The utility of obtaining an ALT in patients >2 to 3 weeks of age, when disseminated
disease is exceptionally rare, is unclear. Clinicians should also keep in mind that elevated transaminase levels in the neonate could result from primary liver disease or from infections such as adenovirus, toxoplasmosis, rubella, or cytomegalovirus.

Given the lack of clear clinical guidelines, and unanswered questions regarding HSV testing, it is understandable that rational clinicians follow variable approaches to febrile or ill neonates. More studies are needed to determine which neonates and young infants require HSV testing and empiric acyclovir. The data suggest that there is risk in ignoring HSV in young neonates who present with fever alone. This must be balanced against the increased cost and risk of nosocomial infection in neonates who have a prolonged length of stay secondary to their HSV evaluation. Hospitals with a longer turn-around time for HSV-related testing may have different approaches to the workup of neonatal HSV. Many laboratories are phasing out viral cultures in favor of PCR-based tests, making the current Red Book recommendation difficult to follow.

To address the aforementioned questions regarding neonatal HSV testing and treatment, pediatric hospitalists may be positioned to play a growing role in studying the problem. Certainly, additional guidance from the American Academy of Pediatrics or Infectious Diseases Society of America has the potential to reduce variation in practice nationally, but the necessary studies on which more refined recommendations are based are yet to be published. At St Louis Children’s Hospital, we have developed a clinical guideline that recommends no HSV testing or acyclovir for neonates and infants that meet the following criteria: nonspecific symptoms starting after 14 days of age, no seizures, no SEM disease, no critical illness, and no cerebrospinal fluid pleocytosis. Before instituting this guideline, practice was variable in regard to this group of patients, with many receiving some combination of HSV testing and empiric treatment. We are currently evaluating this guideline in regard to how or if it has changed practice at our hospital. Similar efforts in other institutions are undoubtedly emerging or established, yet we have little published information to glean from them as of yet. While we wait for better delineation of the value of newer HSV tests, and perhaps the elimination of somewhat impractical (or rarely practiced) recommendations in expert guidelines, pediatric hospitalists may make meaningful contributions to our shared confidence through efforts to standardize local HSV diagnostic and empiric treatment practices and reporting their outcomes. As we typically say at the end of published articles, more studies are needed.

REFERENCES