A 6-day-old boy presents to the emergency department with 1 day of fever and decreased intake. He has no rash, is mildly dehydrated but not ill-appearing, and has normal mental status. An evaluation for serious bacterial infection is performed, but the lumbar puncture is not successful. He receives ampicillin and gentamicin and is admitted to the inpatient unit. The resident team successfully reattempts the lumbar puncture, with 6 white blood cells and >1000 red blood cells. Herpes simplex virus testing of the cerebrospinal fluid and mucous membranes is sent, the patient is started on acyclovir, and his gentamicin is changed to cefotaxime to minimize exposure to nephrotoxic medications. On day 2 of hospitalization, the team notes that his creatinine has increased since admission. This prompts initiation of intravenous fluids and repeat laboratory testing. The parents ask about the potential impact on his future kidney function. The herpes simplex virus testing and all cultures are negative; however, discharge is delayed as repeat creatinine measurements are performed to ensure the creatinine is decreasing.

Neonatal herpes simplex virus (HSV) infections are rare, with an incidence of 9.6 per 100,000 births and a prevalence of 0.2% to 0.3% in febrile neonates. However, neonatal HSV infections are associated with high mortality and, among survivors, long-term morbidity. In the absence of multicenter trials and decision rules, clinicians must rely on findings from published case series, which emphasize that no combination of presenting signs and symptoms can reliably identify all neonates with HSV infection. The variability in presentation has given rise to multiple proposed approaches to empiric testing and treatment and, consequently, substantial variation in the factors that prompt HSV testing, sometimes without clear correlation with known risk factors.

It is important to address this variability in testing and treatment because nonstandardized approaches to testing for HSV are associated with longer lengths of stay and higher hospital charges. Aronson et al reviewed 35,000 emergency department visits for infants younger than 90 days with fever and found that the proportion of infants receiving acyclovir at high-utilizing hospitals was more than double the use at low-utilizing hospitals; overall 32.3% of infants 0 to 28 days and 12.4% of infants 29 to 56 days received acyclovir. Gaensbauer et al, using hospital discharge data, found that acyclovir use increased 60.9% and 82.7% among infants <30 and 30 to 60 days, respectively, between the time periods 1999 to 2005 and 2006 to 2012, without a corresponding increase in the number of infants diagnosed with HSV. These data highlight an opportunity to decrease acyclovir use without causing associated harm.
Beyond the reasonable goal of avoiding unwarranted medication use, the risks of even short courses of acyclovir must also be considered. Extravasation injury, related to acyclovir’s alkaline pH, can cause edema, erythema, pruritus, pain, and skin breakdown,19–21 particularly in neonates,22 which can lead to disfiguring injuries. The nephrotic side effects of acyclovir, thought to be caused by deposition of acyclovir crystals in the kidney,23,24 can occur with brief exposure.25 Nephrotic medication-related acute kidney injury, which increases the immediate cost of care through need for laboratory monitoring and administration of supplemental intravenous fluids, can also cause long-term harm for patients who have the injury early in life.26

No consensus exists on which neonates should be tested for HSV infection and which should be empirically treated with acyclovir. Experts in the field have argued for varied approaches.2,27–29 The lack of agreement among experts likely contributes to the practice variation in diagnosis and management of neonatal HSV, which was reflected in a recent survey of emergency medicine and hospital medicine physicians at our institution. We found variability in factors that prompted testing for HSV (Fig 1) and type of testing performed when considering HSV (Fig 2). The decision to start empiric acyclovir also varied, with 46% treating all who were tested for HSV and 54% treating only those with certain high-risk clinical or laboratory features. Realizing the extent of our local practice variation, we set out to standardize our practice.

One proposed strategy is to universally test and begin empiric acyclovir for all neonates younger than 21 days. Although this approach ensures that virtually all infants with perinatally acquired HSV would receive empiric acyclovir, many infants without HSV would unnecessarily be exposed to the risks of acyclovir. The approach of testing only those with high-risk features is also not satisfying, given the multiple forms of disease presentation, the possibility of nonspecific symptoms at initial presentation, and the consequences of substantial delays in therapy for those infected. Recognition of HSV in a neonate with a vesicular rash and ill appearance is simple, but identifying the neonate with early isolated central nervous system (CNS) disease is less clear-cut. In the case series of 32 patients with HSV by Long et al,29 3 patients presented only with fever and had no cerebrospinal fluid (CSF) pleocytosis, but were ultimately diagnosed with HSV CNS disease. The small size of existing case series makes it difficult to know how many infants ultimately diagnosed with HSV present with nonspecific symptoms. Given the association between increased mortality and delay in initiation of acyclovir,30 waiting for these neonates to worsen and declare themselves before appropriate testing causes unacceptable delay.

A novel option could balance the potential harms of acyclovir with significant delays in diagnosis. At our institution, we have developed hospital-wide consensus based on existing data and our desire to balance benefits and risks of HSV testing and empiric treatment. This reflects provider consensus on empirically treating only those with high-risk clinical and laboratory features. In the approach we are currently implementing at our hospital, all patients younger than 21 days being evaluated for serious bacterial infection will have CSF HSV polymerase chain reaction (PCR) testing performed, but only those with high-risk presenting features (eg, vesicles, ill appearance) or abnormal CSF parameters31 will undergo more extensive testing32 and receive empiric acyclovir therapy. The intended result will be that not every patient tested for HSV will begin empiric acyclovir (although all patients meeting high-risk criteria will receive acyclovir), but, with a rapid HSV PCR turnaround time (15 hours, on average), significant delays in acyclovir

**FIGURE 1** Survey results to identify factors that prompt testing for herpes simplex virus in infants undergoing evaluation for serious infection.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin vesicles</td>
<td>46%</td>
</tr>
<tr>
<td>Seizure</td>
<td>36%</td>
</tr>
<tr>
<td>Maternal history of genital herpes</td>
<td>34%</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>32%</td>
</tr>
<tr>
<td>&lt; 21 days</td>
<td>30%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>27%</td>
</tr>
<tr>
<td>Family history of herpes labialis</td>
<td>26%</td>
</tr>
<tr>
<td>Rash</td>
<td>24%</td>
</tr>
<tr>
<td>Scalp monitor used</td>
<td>23%</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>22%</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>21%</td>
</tr>
</tbody>
</table>

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initiation will be avoided. By tracking all infants younger than 60 days, we intend to decrease overuse in lower-risk and older infants, while providing appropriate testing and therapy to those younger infants at higher risk. Our goal is to improve frontline collaboration with all parties invested in decision-making around management of neonatal HSV.

There are several trade-offs with our proposed approach, particularly for infants younger than 21 days without high-risk clinical or laboratory factors. In this age group, the inclusion of serum HSV PCR testing would ensure identification of infants with disseminated HSV who present with nonspecific symptoms and lack CNS involvement. However, given our aim to limit testing in those deemed to be lower risk, we targeted our testing to isolated CNS disease, as this disease is more often described to present with a paucity of symptoms. Furthermore, approximately two-thirds of infants with disseminated HSV will have CNS involvement, minimizing the number of infants who would be “missed” by this approach. Another potential trade-off is the reliance on PCR testing rather than culture. The sensitivity of HSV PCR tests may vary, depending on primers used and the site of the test. Our laboratory has performed test validation and the results are available in a timely manner. Although surface cultures of skin could potentially increase the sensitivity of our approach in identifying infants with perinatally acquired HSV, trade-offs include increased costs, including discharge delays of HSV-negative infants awaiting culture results.

Having reached consensus, our next aim is to standardize our local practice and disseminate lessons learned after outcome analysis. Recognizing that this is a rare disease and that single-center implementation is unlikely to demonstrate benefit for those infants with HSV, we will also examine outcomes in infants without the disease. Specifically, for infants at low clinical risk, especially those 30 to 60 days of age, we hope these will include decreased acyclovir use and HSV PCR testing. As others have noted, “Just to be safe” is often used as a reason to test and treat our vulnerable children. Paradoxically, this maxim might be undermining the patient safety movement. The time has come to repurpose this powerful phrase as justification for safely doing less.

Although neonatal HSV infection is rare, exposure to testing and treatment is all too common in patients at very low clinical risk; this is only 1 example of many scenarios that fall into the morass of practice variability. Widespread practice variation, especially in disease states of rare prevalence that preclude large-scale trials, has the potential to expose patients to over- or undertesting, and makes meaningful study of outcomes challenging. For this reason, standardizing practice in areas in which evidence is lacking is just as important as standardizing practice in which there is clinical certainty. We respectfully suggest a shift from simple reflection to a focus on purposeful actions to make the system better, and then sharing that experience so we can learn from one another’s successes and failures.

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Testing and Empiric Treatment for Neonatal Herpes Simplex Virus: Challenges and Opportunities for Improving the Value of Care
Laura Brower, Amanda Schondelmeyer, Paria Wilson and Samir S. Shah
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