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COMMENTARY

The Tail Wagging the Dog (or the Challenges Faced When the Financing of Medicine Gets Ahead of the Science of Medicine)

David W. Kimberlin[a]

[a]Division of Pediatric Infectious Diseases, The University of Alabama at Birmingham, Birmingham, Alabama, USA

ABSTRACT In their article in this issue of the *Journal of Clinical Microbiology*, S. R. Dominguez et al. (J Clin Microbiol 56:e00632-18, 2018, https://doi.org/10.1128/JCM.00632-18) describe the performance of PCR detection of herpes simplex virus (HSV) DNA versus viral culture in skin and mucosal samples from 7 neonates with HSV disease. This is a significant contribution to our understanding of the optimal diagnostic approach in babies being evaluated for neonatal HSV disease. Many diagnostic laboratories already have made the change to molecular diagnostics for skin and mucosal swab testing, however, in large part due to the labor costs associated with viral cultures. Thus, important studies such as this one are being conducted to support a decision that has already been made in many locations on mostly economic grounds. This small case series supports the decision to use molecular testing for samples from skin and mucosal sites, but larger studies are needed to more fully define the performance characteristics of PCR in this population. Since a false-positive result would commit a baby to months of management that would be unnecessary and have potential harm, it is critical to base diagnostic decision making on data that support the use of a specific test.

The advent of molecular diagnostics has revolutionized the practice of medicine. No longer is it necessary to grow a pathogen in the laboratory to establish a diagnosis. Now, one can simply detect its DNA or RNA using PCR or other powerful technologies. For herpes simplex virus (HSV) infections, the PCR era was ushered in by Fred Lakeman and colleagues at the University of Alabama at Birmingham in their landmark 1995 publication describing patients with herpes simplex encephalitis (HSE) (1). Prior to that time, the diagnosis of HSE required the patient to have a burr hole drilled through his or her skull so that a piece of (presumably infected) brain could be biopsied and sent to the lab for viral culture. Using stored cerebrospinal fluid (CSF) from HSE subjects whose brain biopsy specimens grew HSV in a treatment study conducted by the Collaborative Antiviral Study Group (CASG) in the 1980s, Lakeman and colleagues proved that viral DNA could be detected in CSF with high reliability. From that point forward, invasive brain biopsies were no longer needed for the diagnosis of HSE. Shortly thereafter, Larry Corey, Anna Wald, and colleagues at the University of Washington published a series of seminal papers documenting the power of molecular test detection of HSV from mucosal samples from women with genital herpes (2–5). Cumulatively, these publications advanced not only the diagnosis of genital and central nervous system (CNS) HSV disease but also our understanding of the natural history of these infections through enhanced detection of the virus at specific anatomic sites down to the single-copy level.

In 1996, colleagues and I published similar work documenting the utility of CSF PCR in neonatal HSV disease (6). Over the next decade, significant advances were achieved in standardizing how PCR at one institution compares with PCR at another. In all of these situations, though, the gold standard against which HSV PCR was compared was viral culture. In the late 2000s, though, things began to change.

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Address correspondence to dkimberlin@peds.uab.edu.

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Clinical laboratories came under increasing financial pressures, at the same time that molecular diagnostics seemed to be entering a golden era. It costs a lot of money in labor to maintain cell lines and to set up and read viral cultures. In contrast, purchasing one PCR machine that can run virtually any highly automated PCR test is less expensive over the long run.

In the case of neonatal HSV CNS disease, there are data that support the use of CSF PCR for diagnosis (6, 7). More recently, smaller studies of blood PCR also have suggested its utility in the diagnosis of neonatal herpes (8–10). However, comparative data on the detection of HSV from skin or mucosal sites in neonatal HSV disease are lacking. Since ~70% of neonatal herpes cases have skin vesicles or mucous membrane lesions and the most common category of neonatal herpes (namely skin, eye, and mouth [SEM] disease) is defined as having solely skin and mucous membrane involvement, knowing how skin and mucosal PCR compares with the gold standard of viral culture is critically important. Diagnostic laboratories have extrapolated from the findings for other populations (e.g., the results for samples from the genital tracts of sexually active adult women) to suggest that PCR, of course, is as good as and is likely better than viral culture of skin or mucous membrane lesions from neonates. That in the process they can save their health care systems money by doing PCRs instead of viral cultures should not be considered coincidental. And they may be right. But there are no data comparing skin and mucous membrane PCR versus viral culture for neonates with HSV disease. The reality is that the economic tail is wagging the health care dog currently, in the hope that molecular diagnostics will work as well in this population as they have in other populations.

With their publication in this issue of the *Journal of Clinical Microbiology*, Dominguez et al. present a retrospective comparison of HSV PCR versus culture for skin and mucosal specimens from neonates with HSV disease (11). They are to be commended for their efforts to inject scientific inquiry into what currently is more of an economically driven calculus. While their report is limited by a sample size of only 7 and by a retrospective study design utilizing frozen specimens, it nevertheless is one of the first to attempt to directly compare PCR with the gold standard of culture in this population. Their results are encouraging. But 7 subjects are not enough to declare equivalence between PCR and culture of samples from skin and mucosal sites of neonates, and the authors are correct to call for larger studies to support their findings. Indeed, the CASG currently is conducting a large, multi-institutional (17 centers) prospective study to define the sensitivity and specificity of PCR versus culture in neonatal HSV disease. In addition, opportunities exist for collaboration between herpesvirologists and leaders of clinical microbiology laboratories at children's hospitals to pool specimens and resources in order to get to more definitive answers more rapidly.

In the absence of these data, though, policy makers have had to adjust their recommendations in the face of the economically driven reality that PCR is more widely accessible than viral culture. In all editions through 2012 of the American Academy of Pediatrics (AAP) Red Book, the Committee on Infectious Diseases (COID) recommended that part of the diagnostic workup for a baby suspected of having neonatal HSV disease include "swab specimens from the mouth, nasopharynx, conjunctivae, and anus ('surface cultures') for HSV culture" (12, 13). With the 2015 Red Book, the recommendation was broadened to include surface swabs "for HSV culture and, if desired, for HSV PCR assay" (14). In the recently published 2018 Red Book, the COID recommends that the physician send surface swabs "for HSV culture (if available) or PCR assay" (15). While the wording changes over this 6-year period may seem small, the intent clearly reflects the increasing difficulty in finding a place to send specimens for viral culture, thereby necessitating a shift to PCR even in the absence of data comparing the two.

The risks of shifting recommendations based upon availability rather than scientific comparison are not inconsequential. While it is likely that molecular detection of HSV will be more sensitive than viral culture in identifying HSV on the skin or mucous membranes of neonates, what if PCR is detecting DNA from nonreplicating virus? Or what if someone in the lab is asymptomatically shedding HSV-1 in their mouth (as 5%

of the world's population is at any given time [16]) and it contaminates a PCR run? Since neonatal HSV infection is a potentially devastating disease, the physician is likely to consider a positive molecular test result as real and to treat accordingly. This includes 14 to 21 days in the hospital, placement of a peripherally inserted central catheter or central line, administration of parenteral acyclovir at a dose that in 20% of cases causes significant neutropenia, continuation of therapy beyond the acute phase with oral acyclovir administered for 6 months, following of absolute neutrophil counts throughout that time, and telling parents that their baby has a viral disease that quite likely came from a sexually transmitted infection—with the associated stresses that all of these place on a family. If the baby really has neonatal herpes, these are very necessary steps to take. If the test was a false positive, it exposes the baby and the family to what are unnecessary risks and harms. With the pace of diagnostic discovery increasing rapidly, now is the time to have more reports such as the one by Dominguez et al. (11) so that decisions can be data driven rather than economically driven.

REFERENCES

1. Lakeman FD, Whitley RJ, National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. 1995. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. J Infect Dis 171:857–863. https://doi.org/10.1093/infdis/171.4.857.
2. Hobson A, Wald A, Wright N, Corey L. 1997. Evaluation of a quantitative competitive PCR assay for measuring herpes simplex virus DNA content in genital tract secretions. J Clin Microbiol 35:548–552.
3. Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. 1997. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. J Clin Invest 99:1092–1097. https://doi.org/10.1172/JCI119237.
4. Wald A, Huang ML, Carrell D, Selke S, Corey L. 2003. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 188:1345–1351. https://doi.org/10.1086/379043.
5. Sacks SL, Griffiths PD, Corey L, Cohen C, Cunningham A, Dusheiko GM, Self S, Spruance S, Stanberry LR, Wald A, Whitley RJ. 2004. HSV shedding. Antiviral Res 63(Suppl 1):S27–S35. https://doi.org/10.1016/j.antiviral.2004.06.005.
6. Kimberlin DW, Lakeman FD, Arvin AM, Prober CG, Corey L, Powell DA, Burchett SK, Jacobs RF, Starr SE, Whitley RJ, The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. 1996. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. J Infect Dis 174:1162–1167. https://doi.org/10.1093/infdis/174.6.1162.
7. Malm G, Forsgren M. 1999. Neonatal herpes simplex virus infections: HSV DNA in cerebrospinal fluid and serum. Arch Dis Child Fetal Neonatal Ed 81:F24–F29. https://doi.org/10.1136/fn.81.1.F24.
8. Cantey JB, Mejias A, Wallihan R, Doern C, Brock E, Salamon D, Marcon M, Sanchez PJ. 2012. Use of blood polymerase chain reaction testing for diagnosis of herpes simplex virus infection. J Pediatr 161:357–361. https://doi.org/10.1016/j.jpeds.2012.04.009.
9. Melvin AJ, Mohan KM, Schiffer JT, Drolette LM, Magaret A, Corey L, Wald A. 2015. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. J Pediatr 166:827–833. https://doi.org/10.1016/j.jpeds.2014.11.011.
10. James SH, Kimberlin DW. 2015. Quantitative herpes simplex virus concentrations in neonatal infection. J Pediatr 166:793–795. https://doi.org/10.1016/j.jpeds.2014.12.077.
11. Dominguez SR, Pretty K, Hengartner R, Robinson CC. 2018. Comparison of herpes simplex virus PCR with culture for virus detection in multisource surface swab specimens from neonates. J Clin Microbiol 56:e00632-18. https://doi.org/10.1128/JCM.00632-18.
12. American Academy of Pediatrics. 2009. Herpes simplex, p 363–373. *In* Pickering LK, Baker CJ, Long SS, Kimberlin DW (ed), Red book: 2009 report of the Committee on Infectious Diseases, 28th ed. American Academy of Pediatrics, Elk Grove Village, IL.
13. American Academy of Pediatrics. 2012. Herpes simplex, p 398–408. *In* Pickering LK, Baker CJ, Long SS, Kimberlin DW (ed), Red book: 2012 report of the Committee on Infectious Diseases, 29th ed. American Academy of Pediatrics, Elk Grove Village, IL.
14. American Academy of Pediatrics. 2015. Herpes simplex, p 432–445. *In* Kimberlin DW, Brady MT, Jackson MA, Long SS (ed), Red book: 2015 report of the Committee on Infectious Diseases, 30th ed. American Academy of Pediatrics, Elk Grove Village, IL.
15. American Academy of Pediatrics. 2018. Herpes simplex, p 437–449. *In* Kimberlin DW, Brady MT, Jackson MA, Long SS (ed), Red book: 2018 report of the Committee on Infectious Diseases, 31st ed. American Academy of Pediatrics, Elk Grove Village, IL.
16. Tateishi K, Toh Y, Minagawa H, Tashiro H. 1994. Detection of herpes simplex virus (HSV) in the saliva from 1,000 oral surgery outpatients by the polymerase chain reaction (PCR) and virus isolation. J Oral Pathol Med 23:80–84. https://doi.org/10.1111/j.1600-0714.1994.tb00261.x.