Clinical Practice Guideline:
During the Emergency Department Evaluation of a Well Appearing Neonate (<30 days of age) with a Fever, Should Empiric Acyclovir be Initiated? (1/11/10)

Reviewed and approved by the AAEM Clinical Practice Committee.

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1. Define the Issue and State the Question

A. Topic Area:

PEDIATRIC FEVER: NEONATAL HERPES INFECTION

B. General Issue:

NEONATAL HERPES INFECTION

C. Specific Question:
DURING THE EMERGENCY DEPARTMENT EVALUATION OF A WELL APPEARING NEONATE (<30 DAYS OF AGE) WITH A FEVER, SHOULD EMPIRIC ACYCLOVIR BE INITIATED?

D. Executive Summary:
The diagnosis and management of neonatal herpes is a complex topic. The clinical decision to consider herpes simplex virus and to initiate antiviral therapy should not be taken lightly, nor should it be avoided given the associated morbidity and mortality. Unfortunately, there is a lack of well-designed clinical research that directly answers the question of whether empiric acyclovir should be initiated during the evaluation of a well appearing febrile neonate (please see **Discussion** for further information).

Currently, this committee advocates the development of institutional protocols that define which neonates require empiric coverage for HSV. In lieu of a developed hospital protocol, the committee advocates the processing of cerebrospinal fluid for HSV PCR and the initiation of acyclovir in any lethargic or toxic appearing neonate and febrile neonates who present with vesicular lesions, disseminated intravascular coagulation (DIC), elevated liver enzymes, or seizures. For the truly well appearing febrile neonate, HSV is a rare entity but requires consideration if there is a CSF pleocytosis.

2. Search

- Define separate strategy for each database / search process used in this review.
- Attach additional search strategies for other database / search process in this review.

SEARCH _1_

A. Keywords used in search:

neonatal herpes AND outcome

B. Database Searched / Process Performed (Ovid, BIOMEDNET, PubMed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

PubMed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **163**

SEARCH _2_

A. Keywords used in search:

acyclovir AND outcome

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **69**

SEARCH _3_

A. Keywords used in search:

empiric acyclovir

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **3**

Additional Search Documentation

SEARCH _4_

A. Keywords used in search:

neonatal herpes AND antiviral

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **282**

SEARCH _5_

A. Keywords used in search:

neonatal herpes AND acyclovir

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **242**

SEARCH _6_

A. Keywords used in search:

herpes encephalitis

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **235**

SEARCH _7_

A. Keywords used in search:

fever AND herpes

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc.):

Pubmed

C. Dates searched: NO Limit

D. Limits applied

HUMANS
ENGLISH
INFANTS / NEWBORNS

E. Final Search Result with # of references **49**

METHODS FOR ARTICLE EVALUATION:

The decision to combine multiple search results was made due to the paucity of directly applicable research articles. In doing so, the goal was to maximize the initial yield and capture all possible articles that addressed the topic. The above-mentioned search results produced **490** unique papers that were then reviewed separately by the committee (two separate physicians). All abstracts were reviewed and each committee member generated a new list of pertinent articles based on the applicability to the topic or the inability to easily access the abstract. After discussion of the divergences between the two separately generated lists, a list of **133** articles was selected. After a significant effort was made to obtain either abstracts or full text from all of the 133 articles, the papers were again re-evaluated separately and the final list of **102** articles was generated. This list included articles that were not easily accessible at the time of the generation of the list.

The full texts of all 102 articles were acquired via the institute's medical library resources. Each committee member then independently evaluated the articles for their relevance to the topic and question and for their quality of evidence. The two separate opinions for each article were then compared and discrepancies were discussed, generating **32** relevant articles from the original 102 reviewed.

Prior to full analysis, a final search of recently published articles (within the last 6 months (January 2008 - July 2008) was done which generated one additional relevant article (Caviness. Cost-effectiveness analysis of herpes simplex virus testing and treatment strategies in febrile neonates. Arch Pediatr Adolesc Med. 2008 Jul;162(7):665-74). Each member of the committee independently assessed this article and deemed it appropriate for inclusion in the analysis, resulting in a combined total of **33** articles.

3. Final Evidence Database – Grade of Evidence Review

- For each reference from step 2, assign a grade of evidence using reference focus, design, and methodology.
- Attach list of final evidence database with assigned grade of evidence.

Grade A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) directly addressing the review issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) indirectly addressing the review issue
Grade C	Prospective, controlled, non-randomized, cohort studies
Grade D	Retrospective, non-randomized, cohort, or case-control studies
Grade E	Case series, animal / model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

4. Final Evidence Database – Quality Ranking

- Critically assess each reference with regards to design and methodology.
- Design Consideration – of the reference under review, consider the focus, model structure, presence of controls, etc.
- Methodology Consideration -- of the reference under review, consider the methodology.
- Attach list of final evidence database with assigned quality of evidence.

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with Possible Bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable / None	Questionable / None	No, either present

List #	Article Information	Grade	Quality
7	Knezevic; Disseminated neonatal herpes caused by HSV1+2; Emerg Inf Dis; 2007	E - Case Report	Adequate
8	O'Riordan; Herpes simplex virus infections in preterm infants; Pediatrics 2006	D - retrospective	Good
10	Verma; Neonatal HSV infection presenting as acute liver failure; J Ped Gastro Nutr; 2006	E - Case Series	Adequate
12	Meyer; Fulminant hepatitis in a newborn with HSV2; Eur J Ped; 2005	E - Case Report	Adequate
18	Fidler; Could neonatal dissem HSV be treated earlier?; Jour of Infect; 2004	E - Case Series	Adequate
23	Langlet; An uncomon case of disseminated neonatal HSV infection presenting with pneumonia and pleural effusions; Eur J Ped; 2003	E - Case Report	Adequate
24	Krolczyk; Opsoclonus: an early sign of neonatal herpes encephalitis; J Child Neuro 2003	E - Case Report	Poor
25	Toth; Neonatal herpes encephalitis: A case series and review of clinical presentation; Can J Neuro Sci; 2003	E - Case Series	Adequate
29	Kimberlin; Natural history of neonatal herpes simplex virus infections in the acyclovir era; Pediatrics 2001	C - prospective	Outstanding
30	Filippine; Neonatal herpes simplex virus infection presenting with fever alone; J Human Virology; 2001	D - retrospective	Adequate

38	Wyckoff; Neonatal herpes simplex virus Type II; 2000	E - Case Report	Adequate
40	D'Andrea; Disseminated herpes simplex virus infecton in a neonate; Am J Emerg Med; 1998	E - Case Report	Adequate
44	Karperien; Case of the month: a newborn with tachypnea and consolidation of the right lung; Eur J Ped 1996	E - Case Report	Poor
45	Jain; Disseminated HSV infection presenting as fever in the newborn; J of Infection; 1996	E - Case Report	Adequate
47	Malouf; Herpes simple virus infections in the neonate; J Ped Child health; 1995	D - retrospective	Poor
48	Elder; Neonatal herpes simplex infection: keys to early diagnosis. J Paediatr Child Health; 1995	D - retrospective	Adequate
51	Greenes; Neonatal herpes simplex virus infection presenting as fulminant liver failure; Ped Infect Dis J; 1995	E - Case Report	Adequate
52	Stanberry; Herpes simplex viremia; report of eight pediatric cases and review of the literature; Clin Infec Dis; 1994	E - Case Series	Poor
53	Shian; HSE in infants and children; Chin Med J; 1994	E - Case Series	Adequate
56	Garland; Neonatal herpes simplex; Royal Women's Hospital 10 year experience with management guidelines for herpes in pregnancy; Aust NZ J Obst Gyn; 1992	E - Case Series	Poor
63	Barker; Primary neonatal HSV pneumonia; Ped Infect Dis J; 1990	E - Case Report	Poor
65	Chang; Evolution of post-natal herpes simplex virus encephalitis to multicystic ecephalopathy; Acta Neuropath; 1990	E - Case Report	Poor
66	Overall; Empiric therapy with acyclovir for suspected neonatal herpes simplex infection; Ped Infect Dis J; 1989	F - Commentary	Poor
70	Koskiniemi; Neonatal HSV infection: a report of 43 patients; Ped Infect Dis J; 1989	E - Case Series	Poor
72	Corey; Difference between HSV type 1 and type2 neonatal encephalitis in neurological outcome; Lancet; 1988	B - randomized	Poor - uses data mining and post-hac eval.
79	McCrossin; Herpes simplex virus encephalitis in children; Medical Journ of Australia; 1986	E - Case Series	Adequate

81	Sullivan-Bolyai; Presentation of neonatal herpes simplex virus infections: implications for a change in therapeutic strategy; Ped Infect Dis; 1986	E - Case Series	Adequate
82	Kishan; Disseminated herpes simplex infection in a newborn- treatment with acyclovir; Indian J Ped; 1985	E - Case Report	Adequate
83	Yag; Fever, seizures in a full-term newborn; Hospital Practice; 1985	E - Case Report	Poor
89	Campbell: A case of neonatal HSV with pneumonia; Can Med Assoc; 1983	E - Case Report	Adequate
92	Prober; Fever in a newborn; CMA; 1982	E - Case Report	Adequate
95	Arvin; Neonatal herpes simplex infection in the absence of mucocutaneous lesions; Journal of Peds; 1982	E - Case Series	Adequate
103	Caviness; Cost-effectiveness analysis of herpes simplex virus testing and treatment strategies in febrile neonates. Arch Pediatr Adolesc Med. 2008 Jul; 162(7):665-74	E - Cost Effective Analysis	Outstanding

5. Assign the Reference Support of the Question

- Separate the references into 3 categories: supportive, neutral, opposed.
- Construct 3 tables assigning the references to the appropriate location using both Grade of Evidence and Quality of Evidence.
- Use lead author name, journal abbreviation, and year of publication as reference.

Supportive Evidence (Article # referenced)

Quality / Grade	A	B	C	D	E	F
Outstanding					103	
Good				8		
Adequate				48	7, 10, 12, 18, 23, 25, 38, 40, 45, 51, 53, 79, 81, 82, 89, 92, 95	
Poor		72		47	24, 44, 52, 56, 63, 65, 70, 83	
Unsatisfactory						

Neutral Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good						
Adequate				30		
Poor						
Unsatisfactory						

Opposing Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding			29			
Good						
Adequate						
Poor						66
Unsatisfactory						

6. Recommendation

- Answer the clinical question if possible.
- Assign a level of recommendation.
- Make a recommendation.

A. Recommendation:

Neonatal Herpes is a historically rare disease; however, due to the profound and significant morbidity and mortality associated with the condition, it carries great weight in the differential diagnosis of a febrile neonate. There is a paucity of well-designed clinical research that directly answers the question of whether empiric acyclovir should be initiated in the emergency department during the evaluation of a well appearing febrile neonate. This clinical guideline aimed at answering this question found no substantial data upon which to base a strong recommendation.

At this point, it is apparent that more research is required. Given the rarity of the disease and the specific population in question, a well-designed and controlled clinical trial would be a Herculean endeavor. Despite this fact, the importance of determining a valid clinical guideline is evident.

During the evaluation of the well appearing neonate (<30 days of age) with a fever, it is the recommendation of this committee that a full sepsis work-up should be done, including blood, urine, and cerebrospinal fluid (CSF) cultures. Empiric antibiotics should then be initiated. Unquestionably, if the patient appears toxic or has a vesicular lesion, empiric antiviral therapy (acyclovir) should be added to the regimen.

For the well appearing neonate presenting with fever alone, debate continues over the decision to initiate empiric antiviral therapy. Several options exist, including waiting for the CSF PCR results or for the development of clinical symptoms prior to starting antiviral therapy. This committee finds both of these options to be undesirable, as they both allow the potential infection to go untreated for an unacceptable amount of time. Another approach is to include empiric antiviral therapy for all febrile neonates after obtaining CSF for HSV PCR. This option would be the most conservative but would inevitably lead to a significant amount of over-treatment of a rare disease. Recently published literature provides some evidence and clinical opinions that support ordering HSV PCR on CSF for those well appearing neonates presenting with fever who are found to have a CSF pleocytosis. It is the recommendation of this committee that acyclovir be initiated on any patient in whom HSV PCR was collected and that the antiviral therapy be continued until the results are known. It would be unwise to not initiate therapy for a potentially life-threatening condition if it was deemed important enough to test for it, especially considering the low side-effect profile of the preferred antiviral therapy.

Given that there is a limited amount of clinical research that corroborates any specific protocol for the empiric use of antiviral therapy in well-appearing febrile neonates, it is prudent for hospitals, pediatric departments, and emergency

departments to develop institutional protocols that help guide clinicians at individual facilities. These protocols could take into consideration the individual institution's prevalence of neonatal herpes, resources for processing CSF for HSV PCR, and likelihood of false positive results. Additionally, it would be advisable to factor in the season during which the patient presents and whether enterovirus infection is more prevalent. Without question, a healthy respect for neonatal HSV infection needs to be maintained; however, its rare occurrence complicates the development of a wholly evidence-based protocol for the administration of empiric antiviral therapy at this time.

B. Level of recommendation:

INDETERMINATE

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A recommended with outstanding evidence	• Acceptable • Safe • Useful • Established / definitive	• Level A / B grade • Outstanding quality • Robust • All positive
Class B acceptable & appropriate with good evidence	• Acceptable • Safe • Useful • Not yet definitive	• Level A / B grade lacking • Adequate to good quality • Most evidence positive • No evidence of harm
Class B 1	• Standard approach	• Higher grades of evidence • Consistently positive
Class B 2	• Optional or alternative approach	• Lower grades of evidence • Generally but not consistently positive
Class C not acceptable or not appropriate	• Unacceptable • Unsafe • Not useful	• No positive evidence • Evidence of harm
Class Indeterminate Unknown	• Minimal to no evidence	• Minimal to no evidence

7. List all conflicts of interest:

NONE

8. Discussion

- Discuss the clinical question and address the issue.
- Make a recommendation and succinctly discuss the rationale and evidence supporting the recommendation.

Physicians who care for pediatric patients have experienced exciting advancements in the evaluation and management of well-appearing febrile children over the past several years. With the continued success of the immunizations for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, the concern for misdiagnosing a febrile infant as having a viral syndrome when in fact a serious bacterial infection exists has been significantly reduced. Unfortunately, this advancement does not apply to the more vulnerable neonatal population (< 30 days of age) in whom a full sepsis work-up, including blood, urine, and cerebrospinal fluid (CSF) cultures, is still warranted. In the neonate with a fever (temperature ≥100.4°F), the clinical decision-making is still seemingly simplistic: full sepsis work-up, initiation of antibiotics, and admission.

The initiation of a full-sepsis work-up on a well-appearing febrile neonate may be reflexive and nearly universally agreed upon; however, the clinical decision-making is not devoid of debate and conflict when the topic of herpes simplex viral infection is addressed. Should herpes simplex virus (HSV) be included in the differential diagnosis? Should the body fluids be tested for HSV? Should empiric acyclovir be initiated while awaiting the results or will the infant suffer deleterious effects because of the delay? Answers to these questions often vary depending on the provider and his or her experiences.

This committee endeavored to determine whether empiric Acyclovir should be initiated on well-appearing febrile neonates while in the emergency department. The incidence of serious bacterial infections in well-appearing febrile neonates (12.6%) approaches that seen in febrile infants 1-2 months old; however, screening protocols to determine low risk patients perform poorly when applied to neonates.[1] Therefore, initiation of empiric antibiotic therapy in this neonatal age group is well supported. What is still questioned is whether the risk of neonatal herpes warrants initiation of empiric antiviral therapy in this population.

Neonatal herpes is by all accounts a rare disease. This is an often written statement, yet the true incidence of the disease is elusive, as neonatal herpes is not a reportable disease and is not tracked nationally. Internationally, the incidence has been found to be ~3-6/100,000 live births[2,3] while in the United States the disease entity appears to be more common. The incidence in the US has been documented as being between 1/2000 to 1/5000 live births and is believed to be increasing.[4,5] While nationally neonatal herpes appears to be more common than internationally, it is still a rare entity in comparison to serious bacterial infections.

Unfortunately, this rare disease is associated with profound morbidity and mortality. Neonatal herpes typically is classified as SEM (Skin, Eye, and/or Mouth) disease, Encephalitis, or Disseminated. Outcomes are influenced by disease classification: SEM is unlikely to lead to death; Herpes Simplex Encephalitis is associated with 15% mortality; and Disseminated HSV is associated with 57% mortality.[6,7,8] The better outcomes associated with SEM disease can partially be attributed to the fact that it is localized and has visible lesions making it easily recognized, aiding in the early administration of antiviral therapy prior to the progression of the disease.

Regrettably, the more concerning varieties, Herpes Simplex Encephalitis and Disseminated Herpes, are the most difficult to diagnosis. Manifestations of these diseases generally occur between the 1st and 2nd week of life but may be delayed until the 4th week of life. As with other neonatal infections, symptoms are most often not specific to the disease and include lethargy, irritability, poor feeding, apnea, and occasionally shock. The telltale vesicular rash that is most often thought of as the hallmark of HSV is not present in a majority of infants initially and only ~50% will go onto develop skin lesions during their disease course.[9,10,11] Concern is enhanced by the fact that the most common form, the Disseminated HSV (accounts for 50% of cases), is the

most deadly form.[12]

Both HSV Encephalitis and Disseminated HSV are elusive and particularly difficult to diagnose early in the disease process. Yet, early initiation of antiviral therapy has been shown to improve outcomes.[8,13,14] It is therefore necessary to maintain a high index of suspicion for these entities in order to improve outcomes. Findings that should heighten the clinician's suspicion for HSV infection are typically stated as being seizures, disseminated intravascular coagulation (DIC), elevated liver function tests, nonspecific symptoms (lethargy, anorexia, fever), and CSF pleocytosis.[15] Other risk factors for neonatal HSV have been found to be first-episode maternal infection in the third trimester, invasive neonatal scalp monitoring, birth before 38 weeks, and maternal age of less than 21 years.[16] Interestingly, knowing that there was no maternal history of HSV does not reduce the risk of neonatal HSV.[9] It has been found that only 12-22% of neonates infected with HSV were born to mothers with a history of genital HSV and only 9% of these mothers had active lesions at delivery.[17,18]

Fortunately, there does exist a safe and effective therapy for HSV that has been studied in several large prospective and double-blinded studies. acyclovir has become the preferred antiviral because of its efficacy and low risk for clinically significant adverse effects.[8,19]

Having established that neonatal HSV infection is rare, devastating, difficult to diagnose, has a safe and efficacious therapy, and benefits from early initiation of antiviral therapy then leads to the question of whether well-appearing neonates presenting with fever alone should receive empiric antiviral therapy. Unfortunately, this committee found a paucity of prospective or randomized trials researching this subject. In an effort to obtain the best available evidence, the search was broadened to include any research pertaining to neonates and herpes or acyclovir with the understanding that this search strategy would include many irrelevant articles. The decision to personally assess close to 500 articles was made in order to capture as many relevant articles as possible. Each article was assessed with consideration of the objective and the particular population. The study population included those neonates who initially presented with fever and had no other significant characteristics (skin lesions, seizures, lethargy, toxicity) that would place HSV infection more prominently on the differential diagnosis list.

Of the 103 reviewed, only 33 articles met our criteria, of which 27 were case reports or case series. The limitations of case reports/series and the inability to generalize them to the larger population inherently weakened the analysis's conclusions. Some interesting themes were found through the evaluation of the case reports/series. At the outset, it was notable that in 21 of the 27 cases reviewed, there was no known maternal history of HSV infection. Another prominent theme that is present within these case reports is the diagnostic dilemma that exists when managing a neonate infected with HSV who initially appears well and has only fever. Many reported a significant delay in the initiation of antiviral therapy with subsequently poor outcomes. The decision to initiate antiviral therapy is made easier when the patient, who was stable upon presentation, becomes unstable or does not improve despite appropriate antibiotics and when blood and CSF cultures remain normal. Unfortunately, these case reports also highlight the profound morbidity and mortality associated with HSV infections. Many specifically advocate for an initial high index of suspicion for HSV infection in this patient population and several also call for empiric antiviral therapy. One retrospective and prospective case series argues that a lymphocytic pleocytosis in a neonate should warrant further investigation for and treatment of HSV until the diagnostic results can substantiate or negate the diagnosis.[20]

This position was supported by the most recent study on the matter that used a theoretical cost analysis to determine which method of evaluation and treatment was most cost-effective, considering both monetary and human life costs.[21] With everything factored into the equation, their recommendation was that empiric antiviral therapy should be initiated on febrile neonates with a CSF pleocytosis and that therapy should be continued until results of CSF HSV PCR are available.

Given that there is a limited amount of clinical research that corroborates any specific protocol for the empiric use of antiviral therapy in well-appearing febrile neonates, it is prudent for hospitals,

pediatric departments, and emergency departments to develop institutional protocols that help guide clinicians at individual facilities. These protocols should take into consideration the individual institution's prevalence of neonatal herpes, resources for processing CSF for HSV PCR, and likelihood of false positive results. The devised protocol for dealing with neonatal HSV management needs to clearly define which neonates should have CSF tested for HSV PCR. As noted previously, any neonate who is toxic appearing or lethargic needs to have HSV infection included at the top of their differential diagnosis list and have antiviral therapy added to their empiric regimen. Those neonates with fever and abnormal liver function tests should also be included. Additionally, it would be advisable to consider the season during which the patient presents and whether enterovirus infection is more prevalent, making the probability of HSV infection lower. After determining that the patient's risk for HSV infection warrants further consideration and testing, a HSV PCR should be sent on the obtained CSF. This committee advocates for protocols to include initiation of empiric antiviral therapy in neonates that have generated enough suspicion on the clinician's part to order the study instead of waiting for results to initiate therapy.

Despite the position of the numerous case reports and few retrospective and prospective studies, a practice guideline recommendation cannot be based upon them without evidence that is more substantial. While the trend does appear to favor a heightened awareness of the disease and early initiation of antiviral therapy, there has not been a prospective analysis of the different management options to make a definitive recommendation. It is the opinion of this committee that due to the rarity of the disease, starting antiviral therapy on all well-appearing neonates would lead to significant unnecessary treatment and potentially prolong hospitalizations while awaiting PCR results. However, because the disease has significant ramifications, and there are agreeing specialists' opinions and theoretical models, this committee advocates for performing HSV PCR on CSF samples and starting empiric antiviral therapy in the emergency department on well-appearing neonates who have a CSF pleocytosis. We would also like to see more investigation comparing the various management options directly in an effort to generate a better-founded algorithm for the evaluation of the well-appearing neonate with fever.

Special Thanks:
The committee would like to extend a special recognition to those who helped to complete this endeavor, including members of the review team and, most notably, Ms. Linda Kesselring, without whom this effort would not have been possible.

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