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### DURING THE EMERGENCY DEPARTMENT EVALUATION OF A WELL-APPEARING NEONATE WITH FEVER, SHOULD EMPIRIC ACYCLOVIR BE INITIATED?

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**Abstract—Background:** Herpes simplex virus (HSV) infection represents significant morbidity and mortality in the neonatal period. Although clear guidelines exist on the evaluation and management of the otherwise well-appearing febrile neonate pertaining to occult serious bacterial infections, there is no standardized approach regarding when to initiate testing and treatment for HSV infection. It is vital we establish a unified guideline based on available clinical research to aid in our decision to evaluate and initiate therapy for this disease. **Methods:** A PubMed search was performed using the keywords “neonate AND fever AND HSV” and “neonate AND fever AND acyclovir.” The time period for the search was May 1982 to May 2016. Identified articles underwent further selection based on relevance to the clinical question. Selected articles then underwent detailed review and structured analysis. **Results:** Our search identified 93 articles, of which 18 were found to be relevant to our clinical question. Recommendations were then made based on thorough review and analysis of the selected articles. **Conclusions:** Neonatal HSV infection carries significant morbidity and mortality if left untreated. High-quality clinical evidence on when to evaluate and treat for possible HSV infection is lacking. Based on available research, HSV infection in the febrile neonate should be strongly considered if age is < 21 days, or if presenting with concerning clinical features. If testing is performed, empiric treatment with high-dose acyclovir should be initiated. Additional research is needed to further clarify which cases mandate evaluation and treatment for HSV, and to better define treatment protocols. © 2017 Elsevier Inc. All rights reserved.

**Keywords—**neonatal fever; febrile neonate; HSV; herpes simplex virus; acyclovir

#### INTRODUCTION

During the assessment of a febrile neonate, defined as < 28 days of age, initiation of a full septic work-up including blood, urine, and cerebrospinal fluid (CSF) analysis followed by administration of broad-spectrum antibiotics is common practice. Consideration of testing and treatment for possible herpes simplex virus (HSV) infection in this situation is a controversial topic lacking evidence from well-designed clinical research.

HSV infection of the newborn is a rare disease in the United States, with an incidence of 9.6/100,000, but it is associated with significant morbidity and mortality (1–3). Historically, HSV has been described with three different clinical manifestations: 1) Skin, Eyes, and Mouth disease; 2) central nervous system (CNS) encephalitis; and 3) disseminated. Skin, Eyes, and Mouth disease is characterized by vesicular lesions without CNS or other organ involvement. Disseminated disease carries the highest mortality and commonly presents in the first week of life with multi-organ involvement and signs of systemic illness (4). CNS infection can present with a more indolent course, typically after the first week of life. The indolent CNS infection is of particular concern given the higher likelihood of initial

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**Table 1. The Definitions of the Grades of Evidence of the Articles**

Grade A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), <i>directly</i> addressing the review issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), <i>indirectly</i> addressing the review issue
Grade C	Prospective, controlled, nonrandomized, cohort studies
Grade D	Retrospective, nonrandomized, 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

presentation, including nonspecific symptoms such as isolated fever (5). Historical features such as maternal history of HSV infection or maternal fever are present only in a minority of cases (5,6).

Due to the variable presentation of this serious disease in neonates, determination of an accepted protocol has been elusive (7,8). No accepted standard currently exists defining the evaluation and management of HSV in a well-appearing febrile neonate. The aim of this statement is to provide emergency physicians with guidance on the evaluation, testing, and treatment of possible HSV infection in neonates presenting with fever alone.

## METHODS

A systematic review of the literature was performed via PubMed search and limited to studies published from May 1982 to May 2016. All studies written in the English language involving human subjects from age zero to 1 month were included. The search was performed using the following terms: “neonate AND fever AND HSV” and “neonate AND fever AND acyclovir.” Three independent physicians reviewed abstracts from all identified articles, and then selected articles for more thorough review based on their relevance to the clinical question. Retrospective studies including case-control and cohort studies, reviews, cost-effectiveness studies, case studies, and prospective studies were included for extensive review. No randomized controlled trials were available for evaluation, and case reports were excluded from detailed analysis.

**Table 2. The Definitions of the Quality Ranking Scores of the Articles**

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

Articles selected for thorough evaluation all underwent a Grade of Evidence Review by all three authors. Each article was assigned a grade based on definitions supplied in Table 1, including research design and methodology. Selected articles were similarly subjected to a quality ranking based on study design quality and methodology, which is outlined in Table 2. More specifically, the quality ranking included design consideration (e.g., structure, presence of controls) and methodology consideration (actual methodology utilized). A summary of a grade of evidence, quality ranking, and article type for each of the selected articles is provided in Table 3.

## RESULTS

Through our search of available literature on HSV infection in neonates presenting with fever, we identified 93 total articles. Of the 93 articles, 18 were found to be relevant to our clinical question and underwent detailed analysis.

The primary goal of this literature review was to determine when testing and treatment for HSV infection should occur in the otherwise well-appearing neonate with fever. Specific considerations included disease epidemiology and severity, treatment efficacy, and the impact of hospitalization length and cost.

### QUESTION 1: WHEN SHOULD TESTING AND TREATMENT FOR HSV BE INITIATED IN A NEONATE PRESENTING WITH FEVER?

Unlike guidelines for the evaluation and treatment of neonatal bacterial infection, the presence of fever or specific age criteria have not been established as necessitating mandatory HSV testing or treatment. Some authors advocate for empiric acyclovir therapy in all febrile neonates based on age alone. Long et al. described an approach in which all febrile neonates with symptom onset at  $\leq 21$  days of age were evaluated and treated for HSV infection (9). This strategy was supported by the high frequency of neonates testing positive for HSV presenting with nonspecific symptoms. Among those diagnosed with CNS disease presenting with nonspecific symptoms, 94% had symptom onset at

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