Clinical Practice Guideline

During the Emergency Department Evaluation of a Well Appearing Neonate with Fever, Should Empiric Acyclovir be Initiated?

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Summary
HSV testing and acyclovir therapy should be considered in the emergency department evaluation of a well appearing febrile neonate especially when presenting with symptom onset ≤ 21 days of age.

Introduction
During the assessment of a febrile neonate, defined as less than 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 standard. 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. 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.

Discussion
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.[1,2,3] Historically, HSV has been described as three different clinical manifestations: (1) skin, eyes, and mouth (SEM), (2) CNS encephalitis and (3) disseminated. SEM is characterized by vesicular lesions absent CNS or other organ involvement. Disseminated disease carries the highest mortality and commonly presents in the first week of life with multiorgan 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 presentation including nonspecific symptoms such as isolated fever.[5]

Due to the variable presentation of this serious disease in neonates, determination of an accepted protocol has been elusive.[6,7] Historical features such as maternal history of HSV infection or maternal fever are present in a minority of cases.[5,8] One large study of neonates with HSV found a lower in-hospital death rate

when treatment was initiated on the first day of hospital admission, as compared to delayed therapy, supporting the use of empiric treatment in suspected neonatel HSV.[9] Symptoms such as lethargy, toxic appearance, seizure, vesicular lesions or laboratory findings such as CSF pleocytosis or elevated liver enzymes should prompt HSV polymerase chain reaction (PCR) testing of blood and CSF as well as testing of mucocutaneous lesions suspicious for HSV. Testing should be accompanied by empiric treatment with acyclovir. Unlike the 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.

Significant advances in diagnostics, specifically the widespread use of PCR testing has improved our ability to accurately identify neonatal HSV infections.[10,11,12] Laboratory cost and turnaround times have improved since the earlier cost analysis published by Caviness et al which showed HSV PCR testing to be cost effective in only those febrile neonates having symptoms consistent with HSV or those with a CSF pleocytosis.[13] Shah et al concluded that the addition of HSV PCR testing increased hospital length of stay (LOS) by 28-39% and that each 12 hour increase in turnaround time led to a 22% increase in LOS, which correlated with increased cost.[14] Large institutions with high volume laboratories may have access to in-house PCR testing, which can result in rapid (< 24 hours) turnaround times. Decreasing turnaround times can potentially eliminate concerns related to prolonged hospitalizations while waiting for PCR testing results. The cost of high-dose acyclovir therapy (60mg/kg/day), treatment of choice for HSV, is low and has been shown to have a favorable side-effect profile although neonatal data is not robust. Previous concerns of acyclovir induced neutropenia and nephrotoxicity with this treatment regimen have been shown to be uncommon.[15,16]

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 ≤ 21 days of age were evaluated and treated for HSV infection. This strategy was supported by the frequency of neonates testing positive for HSV presenting with nonspecific symptoms (50%). Among those diagnosed with CNS disease presenting with nonspecific symptoms, 94% had symptom onset ≤ 21 days of age. Additionally, the frequency of bacterial meningitis previously reported to be (0.4%) and HSV infection (0.2-1.3%) were found to occur at comparable frequency though the overall rate of all types of serious bacterial illness is much higher (14.2%).[17,18]

Conclusion

For the well appearing febrile neonate, HSV infection is a rare entity, but has significant morbidity and mortality if left untreated. Though compelling evidence is not yet available, HSV should be strongly considered in the differential diagnosis, especially those with symptom onset ≤ 21 days of age. Any neonate with seizure, lethargy, toxic appearance, vesicular lesions, CSF pleocytosis or abnormal liver enzymes should have HSV PCR testing of blood and CSF, testing of skin lesions and empiric treatment with high dose acyclovir. Hospital specific protocols are warranted based on testing capabilities given the potential increased cost associated with lengthy turnaround times leading to longer hospitalizations. Additional research is needed to further clarify which cases mandate evaluation and to better define appropriate testing protocols.