

CONTAGIOUS COMMENTS

Department of Epidemiology

THE FEBRILE NEONATE IN THE SUMMERTIME: ENTEROVIRUS OR HERPES?

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Every summer and fall, our hospital sees many newborns with non-specific febrile illnesses. Most of these newborns have a benign and self-limited enterovirus (EV) infection. An occasional neonate will have a more concerning presentation that could still be EV, but might be herpes simplex virus (HSV) or bacterial sepsis. As a result, many febrile newborns this time of year have costly workups including blood, CSF, and urine bacterial cultures, as well as EV and HSV polymerase chain reaction (PCR) assays and viral cultures of multiple specimens. They may be hospitalized for several days or longer pending test results and frequently receive empiric treatment with antibiotics and often acyclovir for extended periods. In situations such as this, syndrome-directed ordering can often guide you to the correct diagnosis in a more timely and cost-effective manner.

This article reviews the clinical syndromes associated with neonatal EV and HSV infections and presents an algorithm for workup of babies in the first month of life.

ENTEROVIRUS

Epidemiology: Approximately 5-15 million symptomatic non-polio EV infections are reported in the US annually, most of which occur from early April-late October. Hospitalization rates are highest for 0-3 month olds. Here at TCH, we see 40 to more than 150 laboratory-confirmed EV cases in children of all ages annually.

Most of these infections are acquired by the fecal-oral route, but respiratory transmission is also documented. Over 70 EV non-poliovirus serotypes are described. They are traditionally classified as the coxsackie A or B viruses, echoviruses, or numbered EVs. Each serotype produces a spectrum of disease but most can also cause a more stereotypic pattern of illness. Multiple serotypes circulate simultaneously, resulting in annual variation in the incidence and spectrum of disease.

Clinical: The most common syndromes associated with EV infection are non-specific febrile illnesses (often associated with rash, respiratory symptoms and diarrhea), hand-foot-and mouth disease characterized by vesicles at these locations, and aseptic meningitis. Less frequently observed are encephalitis, seizures, myocarditis, hepatitis, ocular infections, and pancreatitis. Non-specific febrile illnesses are the most common manifestation at any age. Newborns can present with a sometimes fatal, severe disseminated EV disease mimicking bacterial sepsis or disseminated

HSV infection. Currently there are no approved antivirals available for EV, but a multi-center trial is again evaluating pleconaril for efficacy in neonates with severe EV disease (see box.)

Randomized Trial of Pleconaril v. Placebo for Neonates with Presumed EV Sepsis

Eligibility criteria: Suspected EV sepsis, age ≤ 15 days and symptoms of ≤ 10 days. Contact Amy Stout in TCH Clinical Trials Office (303-864-5642 or 303-855-0028) for more information

Laboratory Diagnosis: Several studies, including our own, demonstrate that detection of EV by polymerase chain reaction (PCR) within 24 hours of specimen collection is associated with decreased length of stay, reduced antibiotic/antiviral use, and lower overall hospital costs.¹ Therefore PCR is the test of choice for the majority of hospitalized patients with suspected EV infection. Newer PCR technology now available at TCH may have an even greater positive impact on outcomes by providing many results within 3-4 hours of specimen receipt, compared to a 1-3 day turnaround time for our prior assay.²

CSF is the highest-yield specimen in young infants with compatible febrile illnesses; blood (serum/EDTA plasma) has been contributory in some studies. Sensitivity of EV CSF PCR is greater than 90% when the clinical picture suggests EV meningitis and the specimen is obtained early in the course of illness. Blood and CSF do not contain EV in the healthy host so a positive result can also be easily interpreted.

CSF parameters should be considered before PCR is ordered. Most infants and older children with EV CNS disease have moderate pleocytosis (a median of 100-500 white blood cells/mm³), although counts can range from zero to a few thousand. Neutrophils may be present early in the course of infection, but lymphocytes predominate later. In newborns with proven EV CNS disease, pleocytosis can be absent in over a third of cases. CSF protein is usually mildly elevated and the glucose concentration is usually normal to low.

THE BOTTOM LINE: Order EV PCR of CSF and blood for suspected EV disease in the febrile neonate, especially if the patient has CSF pleocytosis or severe disease.

Enterovirus 71

Enterovirus 71 is notable for causing severe neurologic disease including a poliovirus-like acute flaccid paralysis, brainstem encephalitis, and cardiopulmonary collapse, although it can also cause hand-foot and mouth disease and aseptic meningitis like other serotypes. EV71 circulated widely in Colorado in 2003 and again in 2005 when 16 infected patients were identified at TCH, 7 of who had adverse neurologic consequences. There was one fatality.³

When severe EV 71 disease is under consideration, separate rectal or throat swabs should be collected for EV PCR, in addition to CSF or blood. This is because severe infection is thought to involve primarily the brain parenchyma so there is little virus in CSF at the time of presentation. Like other EVs though, EV71 is shed at high titer for weeks after onset of symptoms from the throat, and for months from the GI tract, so swabs of these sites are usually positive. Throat and rectal swabs are usually unnecessary for the diagnosis of uncomplicated EV illnesses, moreover they can sometimes be misleading due to prolonged shedding from a prior EV infection or to rhinovirus (which are genetically-related to EV) in the throat. If a diagnosis of severe EV71 disease is being considered, please consult Infectious Disease for assistance.

THE BOTTOM LINE: Send throat or rectal swabs for EV PCR in addition to CSF if severe EV71 disease is suspected. So far this season, no EV71 has been identified.

HERPES SIMPLEX VIRUS

Epidemiology: Unlike EV infections, neonatal HSV is infrequent. Only 800-5000 cases are estimated to occur in the US annually, with fewer than 10 cases typically seen at TCH each year.

Neonatal HSV infections are acquired either *in utero* (5% of cases), perinatally (85% of cases), or post-natally (10%). Important maternal risk factors are the presence of genital lesions at delivery, the type of infection (i.e. primary versus recurrent), duration of rupture of membranes, mode of delivery (cesarean vs. vaginal), and young age of the mother. Unfortunately most (60-80%) HSV-infected babies are born to women without a history of genital HSV or recognizable lesions at the time of delivery, or an obviously-infected sexual partner. Other risk factors for infection include the integrity of the baby's skin (e.g. use of scalp electrodes) or a caregiver with an active HSV lesion.

Clinical: Neonatal HSV is classified as 1) early dissemination involving multiple visceral organs (which can include the brain), 2) CNS disease (with or without skin

lesions), or 3) disease limited to the skin, eye, and/or mouth (SEM disease).

Disseminated HSV disease includes about third of cases and typically presents as a sepsis-like state, often with hepatitis and pneumonia. Another third of infected neonates have CNS disease and present with focal or generalized seizures, lethargy, irritability, tremors, poor feeding temperature instability, and/or bulging fontanelles. SEM infections comprise the remainder, with the majority (80%) having vesicles on initial physical exam. Acyclovir is the initial antiviral of choice but morbidity and mortality is high, particularly for disseminated and CNS disease, even after prompt and appropriate therapy.

Laboratory Diagnosis: The CSF findings in neonates with HSV neurologic disease typically include a mild mononuclear pleocytosis with elevated protein, usually without hypoglycorrhachia. The presence of red blood cells in CSF is not pathognomonic. Some patients with neonatal HSV have normal CSF findings, particularly early in the illness.

At TCH, laboratory diagnosis of neonatal HSV disease can be made by HSV PCR of CSF or of blood, by demonstrating virus in vesicles by direct HSV immunofluorescence (DFA) and culture, or by HSV culture of a multi-source (conjunctival, NP, rectal) swab.

Sensitivity of HSV CSF PCR in neonatal CNS disease ranges from 75%-100% due to variation in the presentation and duration of symptoms at time of specimen collection. Sensitivity of HSV CSF PCR is 93% in disseminated disease and 76% in CNS disease. If CSF is obtained early (i.e. less than 3 days after onset of symptoms) and HSV PCR is negative, a second tap several days later may be informative. Detection of HSV antibodies in blood, or brain biopsy have been helpful in unusual cases. HSV PCR of blood has not been rigorously-evaluated, but has been useful in our experience and in several small series, especially for disseminated disease. DFA of vesicle swabs is about 80% sensitive compared to culture if vesicles are young and adequately sampled. Culture of multi-source swabs can have high yield, particularly in the absence of vesicles.

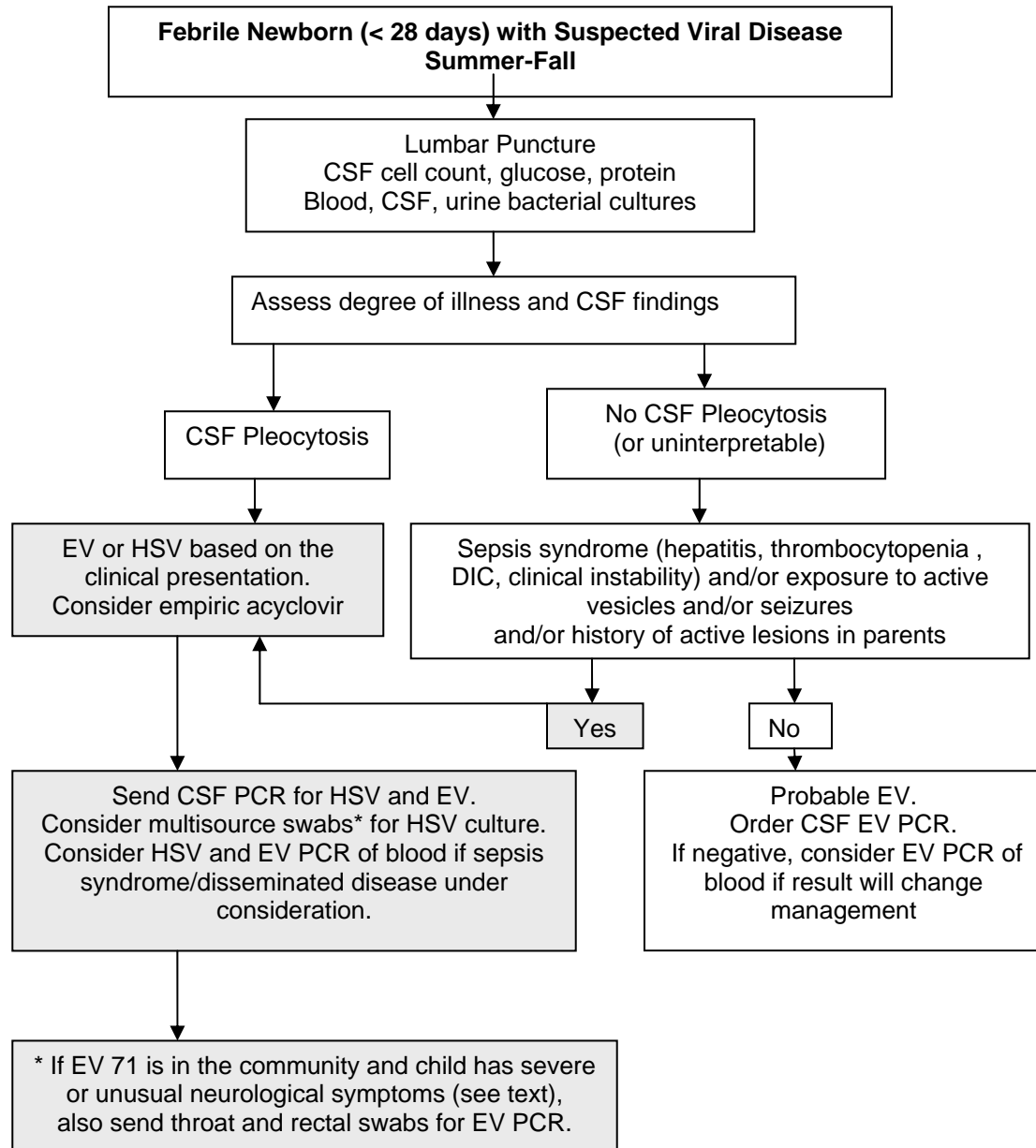
THE BOTTOM LINE: Neonatal HSV is rare but treatable. Have a high index of suspicion in babies with vesicles, who have seizures, or if illness is severe.

RECOMMENDATIONS

The algorithm in Figure 1 depicts our proposed initial workup for neonates with suspected EV or HSV disease. It presupposes that you have initiated antibiotics for patients

with CSF pleocytosis or other signs and symptoms concerning for bacterial sepsis. Table 1 summarizes the specific specimens and available tests for the laboratory diagnosis of neonatal EV or HSV disease at TCH.

Figure1: Proposed diagnostic and therapeutic work up for newborns with suspected viral disease



* See Table 1 for further information

Table 1: Testing for Herpes and Enterovirus at TCH

Virus	Specimens	Test	Schedule	Comment
EV	CSF	EV PCR	Daily	Results in 3-4 hours day shift
	Blood (Throat or rectal swab)*		Mon, Weds, Fri	In by 6 am, results by 3 pm
HSV	CSF or blood	HSV PCR	Daily Mon-Fri	In by 6 am, results by 3 pm. No swabs
	Vesicle swab	HSV DFA & culture	Daily	DFA in by noon, results same day
	Multi-source (eye, throat, rectal) swab	HSV Culture	Daily	Rapid culture results 1 day after inoculation. Final in 7 days

*Send throat or rectal swabs in addition to CSF if EV71 disease is suspected. So far this season, no EV71 has been identified.

FOLLOWUP – THE LAST IS NOT THE LEAST!

Many TCH EV CSF PCR results are now provided within a few hours of specimen arrival in the laboratory. Preliminary bacterial culture results and HSV DFA are available within a day and turnaround time of HSV PCR is more rapid than in previous summers. The clinician's response to these results should likewise be swift.

When the EV CSF PCR is positive and bacterial cultures are preliminarily negative, re-assess the patient promptly. If the patient is improving, as would be expected with EV, consider stopping the antibiotics and acyclovir. Be aware that bacterial and EV co-infections do occur but are rare. Co-infected patients are also expected to have signs and symptoms consistent with bacterial rather than viral infection. Likewise if the HSV PCR is positive, antibiotics can usually be discontinued. If the HSV PCR is negative but the patient has deteriorated or is still concerning for HSV, consider a second lumbar puncture and a repeat HSV PCR.

OUTSIDE THE NEWBORN PERIOD

Enterovirus infections become far more common and HSV less so after the newborn period. The signs and symptoms of HSV encephalitis also become more characteristic and distinguishable from the majority of milder infections caused by EV. Therefore dual orders for HSV and EV PCR and empiric acyclovir treatment should be less frequent in older age groups without focal neurologic signs or evidence of encephalitis.

READING

1. Robinson C., Willis M., Meagher A., Gieseke K., Rotbart H., and Glode M. 2002. Impact of rapid PCR results on management of pediatric patients with enteroviral meningitis. *Pediatric Infect Dis J* 21: 283-86.
2. Kost C.B., Rogers B., Oberste M.S., Robinson C. C., Eaves B.L., Leos K., Danielson S., Weir F., and Nolte F. 2007. A multi-center beta trial of the GenXpert® Enterovirus Assay. *J. Clin. Micro.* 45:1081-86.
3. Perez-Velez C., Anderson M., Glode M., McFarland E., Nix W., Oberste M., Pallansch M., and Robinson C. 2007. Outbreak of poliomyelitis-like paralytic enterovirus 71 disease in Colorado. *Clinical Infectious Diseases*, in press.
4. Rittichier K.R., Bryan P.A., Bassett K.D., Tarrart E.W., Enriquez F.F., Hillyard D.R., Byington C.L. 2005. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatric Infect Dis J* 24:546-50.

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