Should all young febrile infants 60 days of age or younger be tested for enterovirus in CSF with PCR?

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Revised Abstract

Background: Polymerase chain reaction (PCR) testing for enterovirus (EV) in CSF samples has been associated with reduced length of stay (LOS) in young, febrile infants and children with aseptic meningitis, particularly those with CSF pleocytosis. At our institution, collection-to-result turnaround time is ≤ 24 hours. However, there are no definite recommendations that guide its use in various clinical scenarios. We assessed the value of CSF PCR for EV in the evaluation of febrile infants without a source, regardless of CSF pleocytosis and how this management strategy impacts patient care.

Methods: Retrospective medical record review (10/1/09-9/30/10) of infants ≤ 60 days admitted for rule-out sepsis (ROS), including fever without source, apnea, apparent life-threatening event, seizures, and/or any other concerning presentation for which bacterial cultures from 2 sites and treatment with systemic antibiotics were done. Data were cross-referenced with virology records to identify the study population. From a total of 474 infants, 157 (33%) met the study criteria: a) non-bloody CSF sample (<500 red blood cells/ μL) b) no confounding causes of pleocytosis (such as bacteremia, urinary tract infection (UTI), or seizures) , and c) CSF PCR testing for EV.

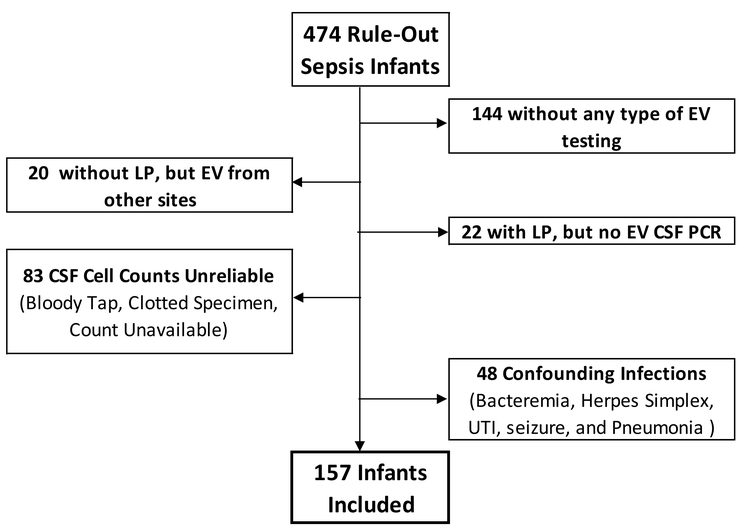
Results: CSF PCR was positive for EV in 33/157 (21%) infants. Of these positive samples, pleocytosis (CSF WBC > 6 cells/μL in infants ≤ 30 d; > 3 cells in those 31-60 d) was absent in 9/22 (41%) of infants ≤ 30 days of age and in 3/11 (27%) of those aged 31 to 60 days. Duration of hospitalization and accrued charges were compared after removing patients who received some or all treatment in the intensive care unit (ICU), underwent surgery, or had their evaluation initiated at another hospital. Compared to those with negative PCR testing for EV in CSF samples, mean length of stay (LOS) and total hospital charges were decreased 0.291 days (p=0.0017) and almost $1000 (p=0.0669), respectively, for the patients. When accounting for ROS evaluations and the presence of fever (either reported or documented), median LOS and total charges were 0.4 days (p=0.0012) and over $700 (p=0.3392) less for the febrile infants whose CSF PCR tested EV positive compared to those with fever who tested negative.

Conclusion: CSF PCR testing for EV in young febrile infants should not be limited to infants with CSF pleocytosis. Consideration should be given to routine testing for EV in all infants ≤ 60 days of age presenting with fever and/or suspected infection regardless of seasonality.

Background & Objective

- PCR testing for EV in CSF samples has been associated with reduced LOS in young, febrile infants and children with aseptic meningitis, particularly those with CSF pleocytosis.
- At our institution, collection-to-result turnaround time is ≤ 24 hours.
- No definite recommendations that guide its use in various clinical scenarios.
- We assessed the value of CSF PCR for EV in the evaluation of febrile infants without a source, regardless of CSF pleocytosis and how this management strategy impacts patient care.

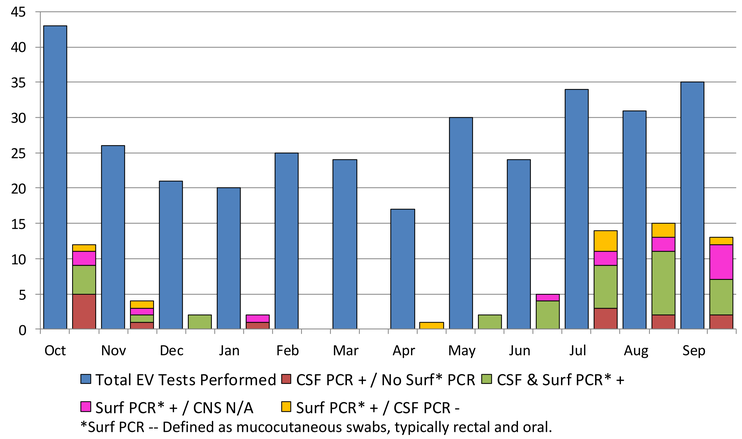
Methods



Results

Total EV Testing & Positive EV Results by Sample Tested

10/01/09 -- 09/30/



*Surf PCR -- Defined as mucocutaneous swabs, typically rectal and oral.

Table 1 Characteristics of Tested Patients

	≤ 30 Days (n=88)		31-60 Days (n=69)	
	CSF EV + (n=22)	CSF EV - (n=66)	CSF EV + (n=11)	CSF EV - (n=58)
Age (days) [Median, IQR]	14.0 [9.5-24.0]	19.0 [11.0-23.0]	45.0 [39.0-54.0]	40.0 [40.0-48.0]
Sex (n; %)				
Male	12 (54.5)	38 (57.6)	8 (72.7)	34 (58.6)
Female	10 (45.5)	28 (42.4)	3 (27.3)	24 (41.4)
Gestation (n; %)				
Term	21 (95.5)	53 (80.3)	2 (18.2)	
Preterm	0 (0)	0 (0)	0 (0)	4 (6.9)
Late Pre-Term	1 (4.5)	10 (15.2)	9 (9.1)	10 (17.2)
Unknown Gestation	0 (0)	3 (4.5)	0 (0)	0 (0)
Febrile (n;%)	22 (100)	45 (68.2)	11(100)	40 (69.0)
ICU Stay (n;%)	0 (0)	5 (7.6)	0 (0)	9 (15.5)
Surgical (n;%)	0 (0)	0 (0)	0 (0)	1 (1.7)*

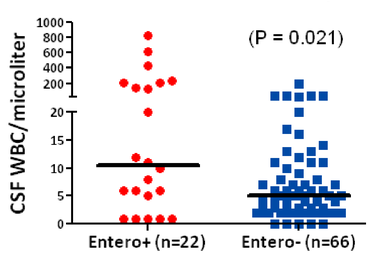
Analysis using Mann-Whitney (rank sum) test

Preterm defined as <34 weeks; Late Pre-term defined as 34 $^{0}/_{7}$ - 36 $^{6}/_{7}$ weeks ; Term defined as ≥ 37 weeks

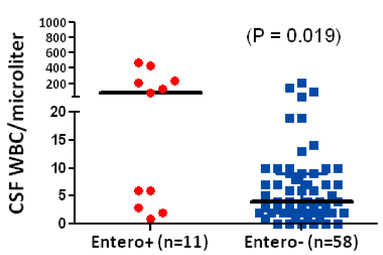
ICU (Intensive Care Unit - Either NICU or PICU); IQR is the Interquartile Range

*Patient found to have pyloric stenosis after ED infectious workup

EV CSF PCR ≤ 30 Days



EV CSF PCR 31-60 Days

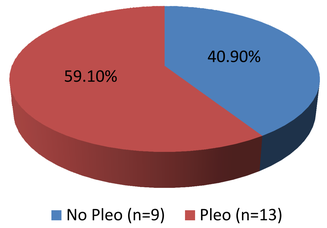


Results

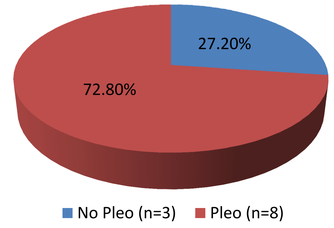
CSF EV Positivity and CSF WBCs

(Pleocytosis defined by the Upper Bound IQR from Kestenbaum 2010 and Internal Controls)

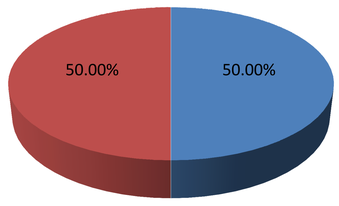
≤ 30 Days - CSF WBC >6
IQR Upper Bound - Kestenbaum 2010[1]



31-60 Days - CSF WBC >3 IQR
Upper Bound -- Kestenbaum 2010[1]



≤ 30 Days - CSF WBC >10.3
IQR Upper Bound - NCH



31-60 Days - CSF WBC >9 IQR
Upper Bound -- NCH

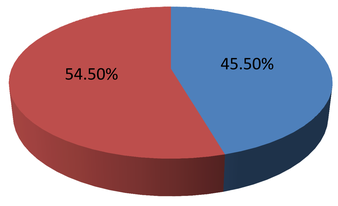


Table 2 Comparing CSF EV + and CSF EV - in ROS Without Confounding Charges or Hospital Days *

	CSF EV PCR + n=28	CSF EV PCR - n=91	P-value
LOS, Days [Median, IQR]	1.7 [1.2-2.2]	2.1 [1.8-2.7]	0.0017
Hospital Charges, US$ [Median, IQR]	7724 [5,947-9,510]	8712 [4,739-8,712]	0.0669

When accounting for ROS evaluations (without confounders) and the presence of fever, median LOS and total charges were 0.4 days (P=0.0012) and over $700 (p=0.3392) less for the febrile infants whose CSF PCR tested EV positive compared to those with fever who tested negative.

Analysis using Mann-Whitney (rank sum) test

IQR is Interquartile Range; LOS is Length of Stay

* Removed patients who had any treatment in the Intensive Care Unit, underwent surgery, or had their laboratory evaluation initiated at another hospital.

Conclusions

CSF PCR testing for EV in young febrile infants should not be limited to infants with CSF pleocytosis. Consideration should be given to routine testing for EV in all infants ≤ 60 days of age presenting with fever and/or suspected infection regardless of seasonality.

References

1. Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics. 2010 Feb;125(2):257-64.

Acknowledgements

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