Enterovirus Meningitis With Marked Pleocytosis

**Introduction:** In neonates and young infants, it can be difficult to distinguish bacterial from aseptic meningitis, especially in the setting of marked CSF (cerebrospinal fluid) pleocytosis. This case series and review of the literature explores the role of early CSF EV-PCR (enterovirus-polymerase chain reaction) in these patients’ diagnostic workup, management, and overall hospital stay.

**Case Series:**

Patient 1 was a 30-day-old female who presented with a fever of 102°F and increased irritability for 1 day. She was admitted to the hospital for an evaluation including complete blood cell count (CBC), blood culture, urine culture, urinalysis, and lumbar puncture (LP). Ampicillin, gentamicin, and acyclovir were initiated. Admission laboratory data included peripheral white blood cell (WBC) count of 9200 cells/µL and a normal urinalysis. Cerebrospinal fluid (CSF) was remarkable for pleocytosis of 1005 cells/µL with 53% lymphocytes, 0 red blood cells (RBCs), protein of 92.8 mg/dL, and glucose of 44 mg/dL (Table 1). Gram-stain of the CSF revealed Gram-positive cocci in pairs; however, no bacteria were cultured. Results of the urine culture were negative. The blood culture grew coagulase-negative *Staphylococcus*, which was believed to be a contaminant. The patient continued to be febrile despite 72 hours of antibiotic therapy. Therefore, a repeat LP was performed, revealing 80 WBC/µL with 63% lymphocytes, 700 RBC/µL, protein of 138 mg/dL, and glucose of 38 mg/dL. Enterovirus–polymerase chain reaction (EV-PCR) performed on the repeat CSF was positive. Herpes simplex virus PCR was negative. Antibiotic therapy was discontinued, and the patient was discharged from the hospital.

Patient 2 was a 7-day-old female who presented with fever of 104°F for 1 day and jaundice. She was transferred from a referring hospital after undergoing an evaluation that included CBC, blood culture, urine culture, urinalysis, and LP. Ampicillin, gentamicin, and acyclovir were begun before patient transfer. WBC count and urinalysis at the referring hospital were reported as normal. Total bilirubin was 9.9 mg/dL. CSF results included 2090 WBC/µL with 53% lymphocytes, 0 red blood cells (RBCs), protein of 92.8 mg/dL, and glucose of 44 mg/dL (Table 1). Gram-stain of the CSF revealed Gram-positive cocci in pairs; however, no bacteria were cultured. Results of the urine culture were negative. The blood culture grew coagulase-negative *Staphylococcus*, which was believed to be a contaminant. The patient continued to be febrile despite 72 hours of antibiotic therapy. Therefore, a repeat LP was performed, revealing 80 WBC/µL with 63% lymphocytes, 700 RBC/µL, protein of 138 mg/dL, and glucose of 38 mg/dL. Enterovirus–polymerase chain reaction (EV-PCR) performed on the repeat CSF was positive. Herpes simplex virus PCR was negative. Antibiotic therapy was discontinued, and the patient was discharged from the hospital.

Patient 3 was a 6-day-old male who presented with fever to 100.8°F for 2 days. He was transferred from a referring hospital after undergoing an evaluation that included CBC, blood culture, urine culture, urinalysis, and LP. Amoxicillin, gentamicin, and acyclovir were begun before patient transfer. WBC count and urinalysis at the referring hospital were reported as normal. Total bilirubin was 9.9 mg/dL. CSF results included 2090 WBC/µL with 53% lymphocytes, 0 red blood cells (RBCs), protein of 92.8 mg/dL, and glucose of 44 mg/dL (Table 1). Gram-stain of the CSF revealed Gram-positive cocci in pairs; however, no bacteria were cultured. Results of the urine culture were negative. The blood culture grew coagulase-negative *Staphylococcus*, which was believed to be a contaminant. The patient continued to be febrile despite 72 hours of antibiotic therapy. Therefore, a repeat LP was performed, revealing 80 WBC/µL with 63% lymphocytes, 700 RBC/µL, protein of 138 mg/dL, and glucose of 38 mg/dL. Enterovirus–polymerase chain reaction (EV-PCR) performed on the repeat CSF was positive. Herpes simplex virus PCR was negative. Antibiotic therapy was discontinued, and the patient was discharged from the hospital.

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**KEY WORDS**

care standardization, clinical, infectious diseases, meningitis, quality improvement systems

**ABBREVIATIONS**

ANC: absolute neutrophil count

CBC: complete blood cell count

CSF: cerebrospinal fluid

EV-PCR: enterovirus–polymerase chain reaction

LP: lumbar puncture

PCR: polymerase chain reaction

RBC: red blood cell

WBC: white blood cell

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198 mg/dL, and glucose of 28 mg/dL (Table 1). CSF Gram-stain was negative. The patient was initially started on intravenous ampicillin, cefotaxime, and acyclovir. Cefotaxime was discontinued in favor of gentamicin. Test results for blood, urine, and CSF cultures remained negative. The patient continued to have fever for 48 hours despite antibiotic and antiviral therapy. A repeat LP showed 130 WBC/µL with 85% neutrophils, 120 RBC/µL, protein of 157 mg/dL, and glucose of 36 mg/dL. Results of the Gram-stain and bacterial culture remained negative. EV-PCR of the CSF was positive. Antibiotic therapy was discontinued, and the patient was discharged from the hospital.

**Question:** How do we currently distinguish aseptic from bacterial meningitis in patients presenting with marked CSF pleocytosis?

**Discussion:** Aseptic meningitis is a common infection among children, with an estimated 75,000 cases each year in the United States. Enterviral infections account for up to 92% of the cases of aseptic meningitis in which an etiologic agent is identified. Enterviral meningitis occurs most often during summer and early fall in temperate climates and usually has a benign course, although some patients develop seizures and coma. The most common entervirus serotypes are Coxsackie B and echoviruses 4, 6, 9, and 11. In enterviral meningitis, CSF analysis shows pleocytosis with a median WBC count of 103 WBC/µL, although reports range from an absence of pleocytosis to >4000 WBC/µL. CSF WBC differential often shows an early dominance of neutrophils with increasing number of lymphocytes as time progresses, but this process is highly variable. CSF glucose and protein are usually in the normal range for a given age. However, hypoglycorrhachia is seen in 5% of patients, and CSF protein is elevated in 39% to 62% of patients. Although bacterial meningitis is far less common than aseptic meningitis, it remains a concern in young children presenting with fever and CSF pleocytosis. In a retrospective study of neonates admitted through a pediatric emergency department, Caviness et al described 204 infants with fever and pleocytosis, of whom 11 (5.4%) had bacterial meningitis compared with 32 (15.7%) with non-herpes simplex viral meningitis. Ten of the 11 infants with bacterial meningitis in this group had >50% polymorphonuclear cells on CSF evaluation. Overall, 14.9% of the 67 neonates with fever, CSF pleocytosis, and polymorphonuclear predominance cells had bacterial meningitis.

In neonates and young infants, bacterial meningitis can be difficult to distinguish clinically from aseptic meningitis. For both entities, fever and irritability are the most common presenting signs in this age range. Signs and symptoms such as meningismus, headache, photophobia, anorexia, and altered mental status are either uncommon or impossible to elicit in neonates. CSF pleocytosis of >1000 cells/µL is typical in bacterial meningitis. A predominance of neutrophils, elevated CSF protein concentration, and decreased CSF glucose concentration are common. However, differentiation between enterviral and bacterial meningitis based on initial CSF analysis can be difficult, with overlap in the expected ranges of WBCs, protein, and glucose in these conditions. Approximately 20% of neonates with bacterial meningitis will have pleocytosis <250 cells/µL, and up to 10% of neonates with enterviral meningitis will show pleocytosis >1000 cells/µL.

In a study of the Bacterial Meningitis Scale, Nigrovic et al evaluated the likelihood of bacterial meningitis based on positive CSF Gram-stain, CSF absolute neutrophil count (ANC), CSF protein, peripheral blood ANC, and history of seizures. A positive CSF Gram-stain was the most sensitive individual test, with 58% of patients with a positive test result having bacterial meningitis. Interestingly, only 9% of patients with a CSF ANC >1000 cells/µL had bacterial meningitis. CSF protein >80 mg/dL, peripheral ANC >10,000 cells/µL, and history of seizures each had

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**TABLE 1** Summary of Patient Laboratory Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, days</th>
<th>WBC, cells/µL (RR: 5–20,000)*</th>
<th>UA</th>
<th>CSF WBC, cells/µL (RR: 0–22,4)*</th>
<th>CSF % Lymphocytes</th>
<th>CSF Protein, mg/dL (RR: 20–170)*</th>
<th>CSF Glucose, mg/dL (RR: 34–119)*</th>
<th>EV-PCR</th>
<th>HSV-PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>9200</td>
<td>Negative</td>
<td>1005</td>
<td>53</td>
<td>92.8</td>
<td>44</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>18,600</td>
<td>Negative</td>
<td>2090</td>
<td>22</td>
<td>145</td>
<td>40</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>7800</td>
<td>Negative</td>
<td>976</td>
<td>5</td>
<td>198</td>
<td>28</td>
<td>+</td>
<td>Not sent</td>
</tr>
</tbody>
</table>

a sensitivity of 2%. Taken as a group, the risk of bacterial meningitis was 0.1% if 0 risk factors were present; this risk increased to 95% if >4 risk factors were present. Applying this scale to our 3 patients, they would have a 27%, 27%, and 3% risk of bacterial meningitis, respectively.

**Question:** Should CSF EV-PCR be used for all neonates and/or young infants presenting with fever and pleocytosis?

**Discussion:** As demonstrated by this case series, CSF EV-PCR offers an additional tool in differentiating bacterial from enteroviral meningitis in neonates and young infants, particularly in the setting of marked CSF pleocytosis. The use of EV-PCR has become increasingly popular over the past decade because it provides rapid, accurate diagnosis and can reduce the use of medical resources for infected patients. EV-PCR methods can now produce results in a matter of hours with a sensitivity and specificity of virtually 100%. Patients with a positive EV-PCR result before hospital discharge have been shown to receive shortened courses of intravenous antibiotics and acyclovir, have significantly fewer ancillary tests performed, have shorter hospital stays, and have a more rapid hospital discharge than EV-PCR-negative patients.

Specifically, patients with positive EV-PCR test results have had a reduction in length of stay of ~30 hours. This finding correlates to a savings of ~$1000 in hospital costs per positive test result. Nigrovic et al. estimated that, given these savings, an enteroviral prevalence of disease of 5.9% in a tested population is required for EV-PCR to be a cost-effective test for utilization in all infants with fever and CSF pleocytosis. Because estimates of enteroviral meningitis in infants with fever and pleocytosis range from 66% to 90% depending on the season, EV-PCR should be cost-effective throughout the year. This efficacy increases as reporting of test results becomes more rapid. Patients with positive EV-PCR results reported <24 hours after specimen collection have had $2798 less in hospital charges than patients with positive results available in >24 hours.

A potential concern for EV-PCR–guided management decisions is that a patient with a positive EV-PCR result may also have bacterial meningitis. We are unaware of any reports of enteroviral meningitis with associated bacterial meningitis. The rate of other concurrent bacterial infections in the setting of a known enteroviral infection is low, with 5.6% of neonates having a urinary tract infection and 1% having bacteremia. In such mixed infections, the clinical presentations are usually severe enough that positive EV-PCR detection is unlikely to deter clinicians from use of antibiotics. Another potential concern is that a false-positive EV-PCR result might allow a well-appearing patient with bacterial meningitis to be discharged. Current EV-PCR systems address the concern of false-positive test results by providing completely self-contained assay cartridges that perform all involved steps, including sample preparation. In evaluation of 1 such kit, 475 CSF specimens were tested, and no false-positive assay results occurred.

**Conclusions:** Year-round, routine use of CSF EV-PCR in all neonates and/or young infants with fever and pleocytosis may be warranted. Use of this technology may be particularly helpful in differentiating enteroviral from bacterial meningitis in patients with marked elevation of CSF WBC count. Justification is particularly strong in populations and seasons with a high prevalence of enteroviral disease. Early differentiation of bacterial meningitis from enteroviral meningitis may decrease iatrogenic risks associated with prolonged hospitalization, will allow decreased use of intravenous antibiotics and antiviral agents, and will produce savings for the health care system largely through decreased length of hospital stays. Positive EV-PCR results may promote earlier discharge and prevent continued evaluation in persistently febrile infants, especially those who are well appearing with a normal peripheral WBC count, normal urinalysis, lack of pretreatment, and with availability of reliable follow-up in their medical home.

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