

Meningitis/Encephalitis Pathogen Panel

The list of pathogens which can potentially cause meningitis, encephalitis, and meningoencephalitis is broad. Early effective therapy for both bacterial and certain viral pathogens has been associated with improved outcomes. Patients whose history, exam, and/or imaging suggests one of these conditions should have a lumbar puncture performed with appropriate diagnostic testing including a cell count with differential, protein, and glucose. Additional tests to consider include bacterial culture, cryptococcal antigen testing, fungal cultures, cultures for acid fast bacilli and/or the new Meningitis/Encephalitis Pathogen Panel.

Nebraska Medicine has recently introduced a new FDA-approved test called the Meningitis/Encephalitis Pathogen Panel (MEPP). This test uses a nested multiplex PCR-approach to amplify DNA targets directly from cerebrospinal fluid (CSF) in patients with signs and symptoms of meningitis or encephalitis. It is able to detect a variety of common bacterial, viral, and fungal pathogens (**Table 1**).

Table 1: Pathogens Detected by Meningitis/Encephalitis Pathogen Panel

Bacteria	Viruses	Yeast
Gram-negative <i>Escherichia coli</i> K1 <i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> Gram-positive <i>Listeria monocytogenes</i> <i>Streptococcus agalactiae</i> (Group B Strep) <i>Streptococcus pneumoniae</i>	Cytomegalovirus Enterovirus Herpes simplex virus 1 Herpes simplex virus 2 Human herpesvirus 6 Human parechovirus Varicella zoster virus (VZV)	<i>Cryptococcus neoformans/gattii</i>

This test is sensitive and very specific (see **Supplementary Table 1** for complete detail), and should only be performed in patients where CNS infection is being seriously considered. Previous studies have shown that using clinical and CSF criteria to determine when to perform PCR testing is unlikely to miss clinically significant results and is highly cost-effective.¹⁻³ For example Wilen, et al.³ restricted herpes virus and enterovirus PCR testing to patients who were: age <2 years, immunosuppressed, or who had >10 WBCs/ μ l. This strategy would not have missed any clinically significant infections in a retrospective review of 366 CSF samples and subsequent implementation of these criteria decreased testing 38-53%. Considering this data it is strongly recommended this test **only** be ordered in the populations listed below. In questionable cases CSF can be saved and the MEPP added on after review of initial testing.

Suggested Criteria for Use of the MEPP: Suspected CSF Infection PLUS

- CSF WBC > 10 nucleated cells/ μ l **OR**
- Age <2 years **OR**
- Immunosuppressed including conditions such as:
 - HIV/AIDS, Organ or bone marrow transplant, Cytotoxic chemotherapy, Use of other immunosuppressive medications (high dose steroids, etc.), or Primary immunodeficiency

Other CSF Tests:

CSF Cultures: The MEPP is not a replacement for CSF bacterial and/or fungal culture but rather is intended to be ordered in conjunction with bacterial culture. If a CSF culture is not ordered and a bacteria or yeast is detected, a CSF culture will be automatically ordered for subsequent isolation and susceptibility testing. It is possible that organisms detected by the MEPP may not be isolated. This may be due to the initiation of antibiotic therapy before lumbar puncture and/or the increased sensitivity of molecular methods.

Herpes Virus Testing: While the herpes viral panel remains available for testing it **should not be ordered when the MEPP has been ordered**. In addition, single tests for the various herpes viruses are available and should be used if follow testing is needed in cases of documented herpes virus infection. It is important to note that the MEPP does not differentiate between active and latent herpes virus infections and treatment decisions should be based on the clinical suspicion of disease.

Encapsulated Bacteria: Only encapsulated strains of *Neisseria meningitidis* and *Escherichia coli* strains that possess the K1 capsular antigen can be detected by this panel.

Cryptococcus: The MEPP has decreased sensitivity for *Cryptococcus* and if this disease is a concern a cryptococcal antigen should be ordered.

Other Organisms: This test does not detect acid fast bacteria or other fungal pathogens and if these are a concern the respective cultures should be ordered. Tests for West Nile, Lyme disease, and syphilis are not included in the panel and should be ordered on the appropriate specimens if these diseases are being considered. Viral culture of CSF will no longer be offered, but individual tests for herpes viruses and enterovirus are still available.

Table 2: Empiric Treatment Recommendations:

Below is a list of suggested empiric treatment recommendations based upon the MEPP results. Antimicrobial choices should be further refined when final susceptibility results return. ID consultation is **strongly** recommended in all cases of meningitis/encephalitis. HHV-6 is a very unusual cause of meningitis/encephalitis but often reactivates in immunocompromised patients. Treatment for this pathogen in particular should only be initiated with input from Infectious Diseases experts.

Pathogen	Recommended Therapy	Comments
<i>E. coli</i>	Ceftriaxone 2g q12h (peds 50 mg/kg q12h) Cefotaxime (neonates only) 50 mg/kg q6h	Primarily neonatal pathogen
<i>Haemophilus influenzae</i>	Ceftriaxone 2g q12h (peds 50 mg/kg q12h)	Rare
<i>Listeria monocytogenes</i>	Ampicillin 2g q4h (peds 75 mg/kg q6h)	TMP/SMX recommended in severe beta-lactam allergy
<i>Neisseria meningitidis</i>	Ceftriaxone 2g q12h (peds 50 mg/kg q12h)	
<i>Streptococcus agalactiae</i> (Group B Strep)	Ceftriaxone 2g q12h (peds 50 mg/kg q12h) Cefotaxime (neonates only) 50 mg/kg q6h	Unusual adult pathogen
<i>Streptococcus pneumoniae</i>	Vancomycin 15-20mg/kg IV q8-12h + ceftriaxone 2g q12h (peds vancomycin 60 mg/kg q6h + ceftriaxone 50mg/kg q12h)	In adults continue dexamethasone.

Pathogen	Recommended Therapy	Comments
CMV	Ganciclovir 5 mg/kg q12h	
HSV-1	Acyclovir 10 mg/kg q8h (peds 20 mg/kg q8h)	
HSV-2	Acyclovir 10 mg/kg q8h (peds 20 mg/kg q8h)	
VZV	Acyclovir 10 mg/kg q8h (peds 20 mg/kg q8h)	
HHV-6	Treatment not generally indicated	If concern for HHV6 infection consult ID
Enterovirus	No effective treatment available	
Human parechovirus	No effective treatment available	
<i>Cryptococcus neoformans/gattii</i>	Liposomal Amphotericin B 3 mg/kg + Flucytosine 50 mg/kg PO q6h	

Empiric Therapy Recommendations for Adult Meningitis: Early initiation of therapy is essential for meningitis as delays in therapy have been associated with mortality and worsened neurologic outcomes.⁴ If LP can be rapidly obtained it is reasonable to delay therapy to improve diagnostic yield of cultures, but if additional diagnostic testing such as a CT is needed antibiotic therapy should be initiated before the LP is performed. Blood cultures should always be obtained before antibiotics are initiated. Therapy choices should be based upon patient risk factors for various pathogens.

Table 3: Empiric Antimicrobial Therapy for Meningitis or Encephalitis

Patient Group (anticipated pathogens)	Recommended Therapy (Adult Dosing Only)
<ul style="list-style-type: none"> Age <1 month 	Ampicillin Plus Cefotaxime*
<ul style="list-style-type: none"> Age ≥1 month and no known immune defect Basilar skull fracture <i>(S. pneumoniae, N. meningitidis)</i>	Vancomycin 15-20mg/kg IV q8-12h PLUS Ceftriaxone 2g q12h
<ul style="list-style-type: none"> Age >50 Impaired cellular immunity: lymphoma, chemotherapy, organ transplant, high dose steroids <i>(S. pneumoniae, L. monocytogenes, gram negative bacilli)</i>	Vancomycin 15-20mg/kg IV q8-12h PLUS Ceftriaxone 2g q12h + Ampicillin 2g q4h
<ul style="list-style-type: none"> Healthcare-associated meningitis due to penetrating trauma or post-neurosurgery <i>(Staphylococci, aerobic gram negatives including P. aeruginosa)</i>	Vancomycin 15-20mg/kg IV q8-12h PLUS Meropenem 2g q8h
<ul style="list-style-type: none"> Meningitis with Severe beta-lactam allergy 	Vancomycin 15-20mg/kg IV q8-12h PLUS Levofloxacin 750 mg TMP/SMX 5 mg/kg q8h (if age >50 or immune impaired) Consult Infectious Disease
<ul style="list-style-type: none"> Encephalitis without Meningitis (fevers and altered mental status) 	Acyclovir 10 mg/kg IV q8h

*Dose based upon age and weight per pediatric dosing guidance in Neofax

References:

1. Hanson KE, Alexander BD, Woods C, et al. Validation of laboratory screening criteria for herpes simplex virus testing of cerebrospinal fluid. *J Clin Micro.* 2007;45:721-4.
2. Lopez Roa P, Alonso R, de Egea V, et al. PCR for detection of herpes simplex virus in cerebrospinal fluid: alternative acceptance criteria for diagnostic workup. *J Clin Micro.* 2013;51:2880-3.
3. Wilen CB, Monaco CL, Hoppe-Bauer J, et al. Criteria for reducing unnecessary testing for herpes simplex virus, varicella-zoster virus, cytomegalovirus, and enterovirus in cerebrospinal fluid samples in adults. *J Clin Micro.* 2015;53:887-95.
4. Auburtin M, Wolff M, Charpentier J, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. *Crit Care Med.* 2006;34:2758.
5. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter Evaluation of the BioFire FilmArray Meningitis Panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Micro.* 2016; posted online 6/22/16.
6. Biomerieux/BioFire Package Insert. 2016.

Supplementary Table 1: Sensitivity of Test for Various Pathogens: (Package Insert Data)^{5,6}

Analyte	Sensitivity/PPA			Specificity/NPA		
	TP/(TP + FN)	%	95% CI	TN/(TN + FP)	%	95% CI
Bacteria						
<i>E. coli</i> K1	2/2	100	34.2-100	1557/1558	99.9	99.6-100
Contrived <i>E. coli</i> K1	47/49	95.9	86.3-98.9	245/245	100	98.5-100
<i>H. Influenzae</i>	1/1	100	-	1558/1559	99.9	99.6-100
Contrived <i>H. influenza</i>	50/50	100	92.9-100	243/244	99.5	97.7-99.9
<i>L. monocytogenes</i>	0/0	-	-	1560/1560	100	99.8-100
Contrived <i>L. monocytogenes</i>	50/50	100	92.9-100	244/244	100	98.5-100
<i>N. meningitidis</i>	0/0	-	-	1560/1560	100	99.8-100
Contrived <i>N. meningitidis</i>	75/75	100	95.1-100	219/219	100	98.3-100
<i>S. agalactiae</i>	0/1	0.0	-	1558/1559	99.9	99.6-100
Contrived <i>S. agalactiae</i>	48/50	96.0	86.5-98.9	244/244	100	98.5-100
<i>S. pneumoniae</i>	4/4	100	51.0-100	1544/1556	99.2	98.7-99.6
Viruses						
CMV	3/3	100	43.9-100	1554/1557	99.8	99.4-99.9
Contrived CMV	47/49	95.9	86.3-98.9	245/245	100	98.5-100
EV	44/46	95.7	85.5-98.8	1507/1514	99.5	99.0-99.8
HSV-1	2/2	100	34.2-100	1556/1558	99.9	99.5-100
HSV-2	10/10	100	72.2-100	1548/1550	99.9	99.5-100
HHV-6	18/21	85.7	65.4-95.0	1532/1536	99.7	99.3-99.9
Contrived HHV-6	50/50	100	92.9-100	243/244	99.5	97.7-99.9
HPeV	9/9	100	70.1-100	1548/1551	99.8	99.4-99.9
Contrived HPeV	50/50	100	92.9-100	244/244	99.5	98.5-100
VZV	4/4	100	51.0-100	1553/1556	99.8	99.4-99.9
Yeast						
<i>C. neoformans/gattii</i>	1/1	100	-	1555/1559	99.7	99.3-99.9