



Syndromic Testing for Infectious Diseases

Part 3: Central Nervous System Infections

HOT TOPIC / 2017

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Disclosures

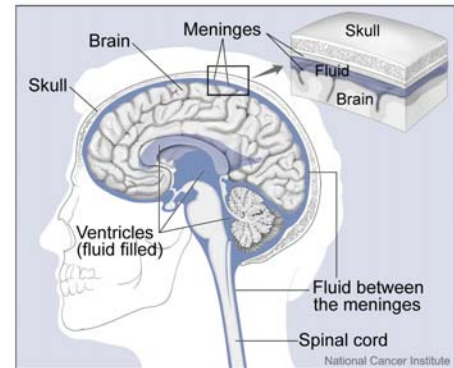
- None

Utilization Message

- As you view this presentation, consider the following important points regarding testing:
 - How is the testing going to be used in your practice?
 - When should the tests be used?
 - How will results impact patient management?

Central Nervous System Infections

- Multiple categories of central nervous system (CNS) infection
 - Meningitis:
 - Inflammation of the meninges
 - Encephalitis:
 - Inflammation of the brain parenchyma
 - Meningoencephalitis:
 - Inflammation of both the meninges and brain
 - Myelitis:
 - Inflammation of the spinal cord
 - Encephalomyelitis
 - Inflammation of the brain and spinal cord



<http://www.cancer.gov/cancertopics/wyntk/brain/>

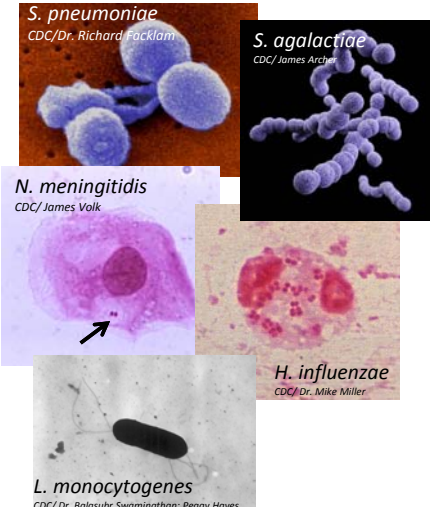
Meningitis vs. Encephalitis

- Symptoms are nonspecific and may overlap
- Causes of CNS infection may be bacterial, viral, fungal, or parasitic
- Noninfectious causes of CNS disease should also be considered

	Meningitis	Encephalitis
Fever	Yes	Yes
Headache	Yes	Yes
Nausea/Vomiting	Yes	Yes
Photophobia	Yes	No
Neck Stiffness	Yes	No
Altered Mental Status	No	Yes

Common Causes of CNS Infection

Bacterial



S. pneumoniae
CDC/Dr. Richard Facklam

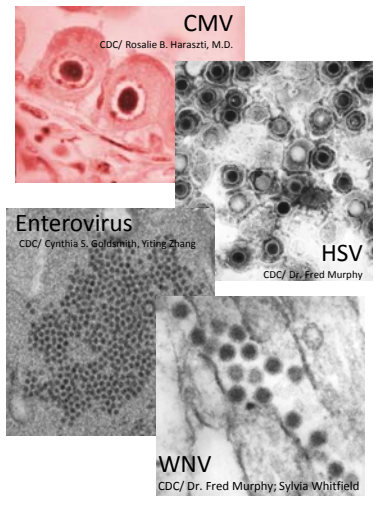
S. agalactiae
CDC/James Archer

N. meningitidis
CDC/James Volk

H. influenzae
CDC/Dr. Mike Miller

L. monocytogenes
CDC/Dr. Balasubramanian; Peggy Hayes

Viral




CMV
CDC/ Rosalie B. Haraszi, M.D.

Enterovirus
CDC/ Cynthia S. Goldsmith, Yiting Zhang

HSV
CDC/ Dr. Fred Murphy

WNV
CDC/ Dr. Fred Murphy; Sylvia Whitfield

Fungal



Cryptococcus spp.
CDC/ Dr. Leonor Haley

All images from <https://phil.cdc.gov/phil>

Diagnosis of CNS Infections

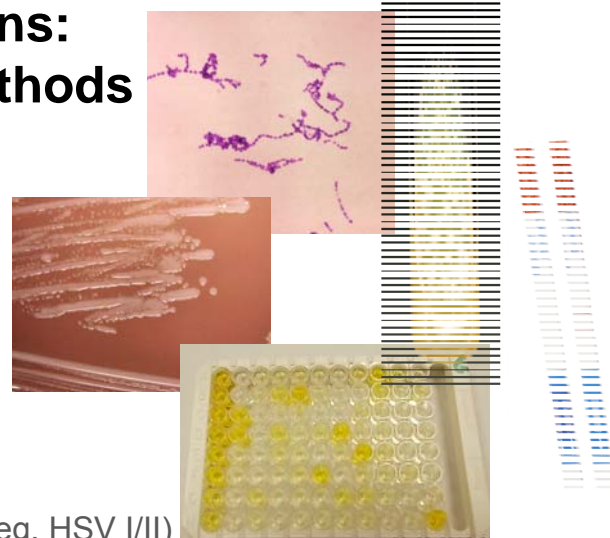
- Differential diagnosis can be narrowed by:
 - Careful clinical evaluation (eg, symptoms, exposure history and season, vaccination history, immune status)
 - Evaluation of cerebrospinal fluid

CSF Findings	Infectious Causes of CNS Infection			
	Normal	Viral	Bacterial	Fungal/Tb
Appearance	Clear	Clear	Turbid	Variable
Opening Pressure (mm H ₂ O)	100-180	100-300	200-500	150-340
Total White Blood Cells (cells/μl)	0-5	5-1000	100->1000	5-1000
Protein (mg/dL)	≤30	30-300	60-500	>60
Glucose (% of blood glucose)	≥60%	≥60%	≤45%	≤45%

- Dedicated microbiologic testing necessary to establish definitive diagnosis

Diagnosis of CNS Infections: Traditional Laboratory Methods

- Bacterial or Fungal Agents
 - Gram and fungal stains
 - Culture
 - Antigen detection:
 - *Cryptococcus* species
 - *Streptococcus pneumoniae*
- Viral Agents
 - Culture
 - Singleplex molecular approaches (eg, HSV I/II)
 - Serology (eg, Neurotropic arboviruses)



<https://phil.cdc.gov/phil/>

Meningitis and Encephalitis Panel (MEP)

- Filmarray MEP (BioFire) FDA-approved in 2015
- Includes 14 targets:

Bacterial

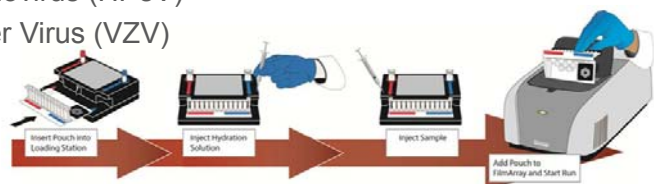
- *E. coli* K1
- *H. influenzae*
- *L. monocytogenes*
- *N. meningitidis*
- *S. agalactiae*
- *S. pneumoniae*

Viral

- Cytomegalovirus (CMV)
- Human herpes virus 6 (HHV-6)
- Human parechovirus (HPeV)
- Varicella Zoster Virus (VZV)
- Enterovirus
- HSV-1
- HSV-2

Fungal

- *Cryptococcus* species



<http://www.biofire.com/products/filmarray/>

Case Studies

The Meningitis/Encephalitis Panel: To Use or Not to Use?

Case #1

- 20-year-old male presents with sudden onset fever, headache, neck stiffness and photophobia. He indicates that he recently returned from a mission trip to Mali. He is otherwise healthy, though he has missed all recommended vaccines after the age of 8.
- CSF was collected and was cloudy with elevated protein and 150 white blood cells (WBCs)/ μ L. CSF glucose was 20% of his blood glucose.
 - *Should the MEP be performed in this patient?*

Case #1 Resolution

- Findings are suggestive of bacterial meningitis
 - Travel to the 'meningitis-belt' in Africa
 - Incomplete vaccination against *N. meningitidis*; no booster for *S. pneumoniae*
- MEP would be appropriate as a first-line test for this patient as the differential for bacterial meningitis is broad



<https://wwwnc.cdc.gov/travel/diseases/meningococcal-disease>

Case #2

- HIV-positive patient (105 CD4⁺ cells/ μ L) presents with photophobia, headache, fever, and progressive, unintentional weight loss. Patient indicates that he recently helped his local church clean the bell tower, which was covered with bird droppings.
 - Should the MEP be performed in this patient?*

Case #2 Resolution

- Presentation, risk, and exposure suggestive of cryptococcal meningitis
- Perform *Cryptococcus* antigen (CrAg) test on CSF and serum first
 - CrAg detection is rapid, sensitive and inexpensive
- MEP could be considered if the CrAg is negative.



Advantages of Syndromic Panel Testing for Meningitis and Encephalitis

- Broad panel
 - Inclusion of agent for which routine testing is not available (eg, HPeV)
- Rapid test-to-result turnaround time compared to standard methods (eg, culture)
- Potentially more sensitive in patients who received antibiotics prior to CSF collection
- Rapid assay with minimal technologist hands-on time

Limitations of Syndromic Testing for Meningitis and Encephalitis

- Cost
 - Targeted testing may be more appropriate in certain cases
- Broad, but ***not*** all inclusive!
- Interpretation of positive results may be challenging
 - HHV6 – Germline integration vs. genuine cause of CNS disease
 - *S. pneumoniae* – False-positive results have been reported
 - ≥ 2 targets detected
- CSF Gram and fungal stains and culture are still required
 - Susceptibility testing, public health laboratory requirements

References

- Leber AL, Everhart K, Balada-Llasat JM, et al. 2016. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol* 54:2251-2261.
- Rhein J, Bahr NC, Hemmert AC, et al. 2016. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. *Diagn Microbiol Infect Dis* 84:268-273.
- Graf EH, Farquharson MV, Cardenas AM. 2017. Comparative evaluation of the FilmArray meningitis/encephalitis molecular panel in a pediatric population. *Diagn Microbiol Infect Dis* 87:92-94.



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