Updates on Diagnosis of Meningitis and Encephalitis

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Disclosure/Disclaimer

• **Relevant conflict of interest**
  – None

• **Disclaimer**
  • The views expressed in this lecture are my personal scientific opinions, and do not necessarily reflect the position or policy of the Department of Veterans Affairs.
Educational Objectives

• Describe importance of disease recognition and timely diagnosis in meningitis and encephalitis
• Describe epidemiology of meningitis and encephalitis in US
• Describe the advantages and limitations of new diagnostic modalities for CNS infections
Today’s Outline

• Review of Basic Concepts in CNS Infections
• Updates on Epidemiology in Adult Population:
  – Community-Acquired Meningitis
  – Encephalitis
• Diagnostic Strategies in CNS Infections
  – Are Newly Available Molecular Diagnostics Game Changers?
Case Presentation

- 22 year-old previously healthy male college student was admitted to the hospital because of fever, vomiting, and altered mental status.
- He had been well until 5 days earlier, when cough, sore throat, and rhinorrhea developed.
- On the evening before admission, he developed acute fever up to 39.4 with mild headache.
- At noon on the following day, he began to have worse headache and vomit. Taken to ER by roommate at 6:00PM.
- Upon arrival to ER, he was lethargic and oriented for name and place, but not for time.
• 45 min after arriving to ER, he suddenly developed grand mal seizure.
  – Funduscopic exam suggested elevated intracranial pressure.
  – CT scan showed diffuse cerebral edema with herniation.

• Scattered purpura started to appear in extremities.
• Rapid progression of hypotension with 3 maximized pressors
• Ventriculostomy was placed (opening pressure 35 cm H2O).
• The patient passed away at 8:00AM.
• Autopsy result:

  **Meningococcal Meningoencephalitis**
Potential Severity: Severe to Catastrophic

- Unique Aspects of CNS
  - Lack of regeneration capability
    - Very specific function in each region
  - Encased in tight bony structure (skull and spinal canal)
    - Vulnerable to increased pressure
    - Unable to visualize or palpable from outside
    - Absence of physiologic “drainage” mechanism
    - Physiology with acute inflammation can progress very rapidly

Bacterial meningitis remains one of the most feared and dangerous infectious diseases that a physician can encounter.
CNS Infections (Definitions)

- MENINGITIS
- ENCEPHALITIS
- MENINGOENCEPHALITIS
- BRAIN ABSCESS
- SUBDURAL/EPIDURAL ABSCESS
- SPINAL CANAL ABSCESSES

Netter’s Neurology 2nd ed. Saunders 2012
Few Important Basics

1. Blood-Brain Barrier

- Selective barrier formed by endothelial cells of blood vessels in CNS
- Three major locations:
  1. Arachnoid epithelium (subarachnoid space and brain/spinal cord parenchyma)
  2. Meninges surface
  3. Choroid plexus
- Physiologic mechanism to protect CNS from acute physiologic status change and toxin exposure

Few Important Basics

1. Blood-Brain Barrier

Serum and CSF Concentration of Penicillin in Meningitis

- Lipopolysaccharide and multiple cytokines affect BBB function and integrity
- Some medications can cross BBB only in the presence of inflammation (examples):
  - Penicillins
  - 3rd/4th generation cephalosporins
  - Vancomycin

Serum Concentration
CSF Concentration

Few Important Basics

2. Sources of Infection

- CNS is in completely enclosed sterile space
- Three major routes of infection:
  - **Hematogenous**
    - Vast majority of community-onset bacterial CNS infections
  - **Contiguous**
    - Direct extension from neighboring anatomical sites
    - Usually has clue in history of illness
      - Recent trauma/surgery to skull or spine
      - Recurrent CNS infections
      - Severe infection in sinus or middle ear
  - **Ascending**
    - Direct extension from peripheral nervous system
    - Usually viral (e.g. HSV)
2. Sources of Infection

- Relatively few pathogens can survive in bloodstream and have affinity to meninges and brain (i.e. hematogenous pathogens)
  - Encapsulated organisms
    - *Neisseria meningitidis*
    - *Streptococcus pneumoniae*
    - *Haemophilus influenzae*
    - *Cryptococcus neoformans*
  - Intracellular organisms
    - *Listeria monocytogenes*
    - Enterovirus group
    - Arbovirus group

Immunologic defects against these organisms (e.g. complement deficiency, cellular immunodeficiency) can lead to higher risk

3. Typical Time Course of Neurologic Disorders

<table>
<thead>
<tr>
<th>Focal</th>
<th>Acute (Hours)</th>
<th>Subacute (Days)</th>
<th>Chronic (Weeks-Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular (arterial or venous)</td>
<td>•</td>
<td></td>
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<tr>
<td>Traumatic</td>
<td>•</td>
<td>• Vascular (venous)</td>
<td>• Brain abscess</td>
</tr>
<tr>
<td></td>
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<td>• Brain abscess</td>
<td>• Tumor</td>
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<tr>
<td></td>
<td>• Brain abscess</td>
<td>• Spinal abscess</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-focal</th>
<th>Acute (Hours)</th>
<th>Subacute (Days)</th>
<th>Chronic (Weeks-Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis (bacterial)</td>
<td>•</td>
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</tr>
<tr>
<td>Toxic/Metabolic</td>
<td>•</td>
<td>• Encephalitis</td>
<td>• Degenerative</td>
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<td></td>
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DISEASE RECOGNITION AND EPIDEMIOLOGY OF MENINGITIS AND ENCEPHALITIS
Community-Acquired Meningitis

Disease Recognition

Aseptic Meningitis

- >80% of meningitis cases
  - Typically preceded by URI or nonspecific viral syndrome for 1-2 wk
  - Patients are usually appearing benign with no hemodynamic instability
  - Nearly always alert & oriented

- Typical symptoms
  - Moderate-severe headache
  - Photophobia
  - Neck stiffness
  - Generalized myalgia

- Usually self-limited disease

Bacterial Meningitis

- ~10% of meningitis cases
  - Often abrupt onset
  - May or may not have preceding symptom
  - Rapid progression of symptom
  - Altered mental status and hemodynamic instability are very common

- Typical symptom
  - Severe headache
  - Fever
  - Neck stiffness
  - Altered mental status

- Uniformly fatal if untreated
# Disease Recognition

## What are Common Symptoms in Bacterial Meningitis?

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Headache</td>
<td>80-95%</td>
</tr>
<tr>
<td>Fever</td>
<td>90-95%</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>80-90%</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>70-80%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20-50%</td>
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**Classic Triad (Fever/Nuchal Rigidity/Altered Mental Status):** 30-45%

**At Least 2 of Classic Triad:** >95%

*References*

Etiologies of Community-Acquired Meningitis

- **Viruses**
  - Enteroviruses
  - Arboviruses
  - Herpesviruses
  - Lymphocytic choriomeningitis virus
  - Human immunodeficiency virus (HIV)
- **Bacteria**
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
  - *Streptococcus pneumoniae*
  - *Listeria monocytogenes*
  - *Escherichia coli*
  - *Streptococcus agalactiae*
  - *Klebsiella pneumoniae*
  - Rickettsiae
  - *Mycobacterium tuberculosis*
- **Spirochetes**
  - *Treponema pallidum* (syphilis)
  - *Borrelia burgdorferi* (Lyme disease)
  - *Leptospira* spp.
- **Protozoa and Helminths**
  - *Naegleria fowleri*
  - *Angiostrongylus cantonensis*
  - *Strongyloides stercoralis* (hyperinfection syndrome)
- **Noninfectious Causes**
  - Intracranial Tumors and Cysts
  - Medications
  - Autoimmune diseases
    - Systemic lupus erythematosus
    - Behçet’s disease
    - Sarcoidosis
    - Vogt-Koyanagi-Harada syndrome
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Community-Acquired Meningitis

- Epidemiology of community-acquired meningitis has changed greatly over years:
  - Aging society
  - Increasing number of population with risk factors
  - Vaccinations
    - *Haemophilus influenzae* type b vaccine
    - Quadrivalent meningococcal vaccine
    - Pneumococcal vaccines
    - Mumps/Measles/Rubella vaccine
  - Declining TB prevalence in US
  - Emergence of new pathogens
    - West Nile Virus
Etiology of Bacterial Meningitis in US

Pneumococcus is by far the most common bacterial pathogen. *H. influenzae* and meningococcus had declined; *L. monocytogenes* remain the same.

Bacterial Meningitis

Microbiology Based on Risk Factors

- < 1 month
  - Group B strep
  - E. coli
  - Listeria
  - S. pneumoniae
  - N. meningitidis
  - H. influenzae

- 1-23 month
  - Group B strep
  - E. coli

- 2-50 years
  - S. pneumoniae
  - N. meningitidis

- > 50 years
  - Listeria
  - S. pneumoniae
  - N. meningitidis

- Immune suppressed
  - Listeria
  - S. pneumoniae
  - N. meningitidis
  - Aerobic GNR

**Basilar skull fracture**
- S. pneumoniae
- "CSF leak"

**Neurosurgery**
- S. aureus
- S. epidermidis
- Aerobic GNR

**"Think of commensal flora"**

- Neonates: Vaginal flora may include group B streptococcus and Listeria monocytogenes
- Neurosurgery: skin and hospital environment
- Basilar skull fracture: oropharyngeal flora

Credit: Drs. Judy Streit and Birgir Johannsson
Community-Acquired Meningitis

Microbiology Based on Presentation/Risk Factors

- **Bacterial**
  - Humoral immunodeficiency
    - Asplenia
    - Complement deficiency
    - Hypogammaglobulinemia
  - Head trauma
  - Neurosurgery

- **Viral**
  - Seasonality (more in summer)
    - Enteroviruses
  - Sexual history
    - HIV
  - Outdoor exposure/travel
    - West Nile Virus

- **Fungal**
  - Cellular immunodeficiency
  - TNF-alpha blocking therapy

- **Tuberculous**
  - Slow progression
  - Exposure to tuberculosis
  - Immigration from high-prevalence countries
  - Incarceration
  - Cellular immunodeficiency
  - TNF-alpha blocking therapy

- **Other**
  - Outdoor exposure
    - Rickettsia
    - Lyme disease
Disease Recognition of Encephalitis 
Compared to Meningitis

Brain Parenchymal Involvement
- Focal neurologic sign
  - May present as character/personality change
- Altered mental status
  - Coma or obtundation is more common and appears in early stage

Meningeal Irritation
- Neck stiffness is less common
- Headache may or may not present

Other clues:
- Outdoor exposure (West Nile Virus, Rickettsia)
- Animal exposure (Rabies, Leptospilla)
- Travel history (Japanese Encephalitis, Yellow Fever)

Suspect encephalitis for any unexplained brain parenchymal lesion Especially when not consistent with neurovascular anatomy
Major Pathogens of Encephalitis

- **Bacterial (usually as meningoencephalitis)**
  - *Neisseria meningitidis*
- **Bacterial (purely as encephalitis)**
  - *Listeria monocytogenes*
- **Parasitic**
  - Amoeba meningoencephalitis

- **Viral (most common)**
  - HSV
  - VZV
  - HHV-6/HHV-7
  - Arboviruses
  - West Nile Virus

>80% of Encephalitis is Idiopathic (unknown etiology)

**Important Points in ER:**

1. Recognize clinical syndrome and suspect encephalitis
2. Not to miss less common but treatable causes (HSV and bacterial)


**Encephalitis**

**Diagnostic Clue in History**

- **Seasonality**
  - Summer/Fall
    - West Nile virus
    - Arbovirus infections
      - St Louis encephalitis virus
      - Eastern equine encephalitis virus
      - California encephalitis viruses
      - Western equine encephalitis virus
  - Winter/Spring
    - Measles
    - Mumps
  - Any Season
    - HSV-1
    - HIV infection

- **Anatomical site of infection**
  - Temporal lobe
    - HSV-1
  - Basal ganglia
    - Arbovirus infections

- **Travel history**
  - Japanese encephalitis
  - Yellow fever
  - Zika virus

- **Animal exposure**
  - Rabies
HSV Encephalitis

Clinical Presentation

- One of few “treatable” cause
- Typically involves temporal lobe
  - T2 high intensity on MRI
  - Low density on CT
- Classical presentation:
  - Fever and personality change
    - Almost uniformly present
  - Seizure
  - Aphagia
  - Motor deficit
- CSF HSV PCR has very high sensitivity and specificity, but can be negative in very early phase
DIAGNOSTIC STRATEGIES IN CNS INFECTIONS
CNS Infection

General Principles of Diagnostic Approach

Accurate Diagnosis
Effective Use of Resource

Timely Management
Consequence of Mismanagement

Most important question in ER:
“Am I Missing Bacterial Meningitis?”
Approach to Possible Bacterial Meningitis

Time is Money!!

- Many studies indicated that delay of antibiotic therapy leads to higher mortality and morbidity
- Sterilization of CSF takes several hours to occur after antibiotics

Always try to initiate antibiotic therapy ASAP!!

Case fatality rate according to door-to-antibiotic time interval in adult acute bacterial meningitis

Evaluation of Acute Meningitis

Physical Examination

- **DO NOT MISS MENINGEAL IRRITATION**
  - Nuchal rigidity (moderate sensitivity; moderate specificity)
  - Kernig's/Brudzinski’s sign (low sensitivity; high specificity)
  - Jolt accentuation (high sensitivity; low specificity)

- **DO NOT MISS INTRACRANIAL HYPERTENSION SIGN**
  - Funduscopic examination
  - Bulging of anterior fontanelle (infant)

- **DO NOT MISS FOCAL NEUROLOGIC SIGN**
  - Check level of consciousness (alertness and orientations)
  - At minimum, examine cranial nerves and motor/sensory of extremities
Evaluation of Acute Meningitis

Papilledema

Normal Fundus

Papilledema due to Meningitis

http://webeye.ophth.uiowa.edu/eyeforum/atlas/index.htm
Evaluation of Acute Meningitis

Lumbar Puncture

• Single Most Important Diagnostic Test for Meningitis!!
  – “Must DO” diagnostic procedure whenever meningitis or encephalitis is suspected clinically

• Contraindications:
  – Intracranial mass lesion
  – Intracranial hypertension
  – Severe thrombocytopenia or coagulopathy
  – Agitated patient
Evaluation of Acute Meningitis

CSF Examination

Routine CSF Tests
• Opening pressure
• Cell count with differential
• Glucose
• Total protein
• Gram stain
• Bacterial culture

Based on Clinical Context
• AFB smear/culture
• Fungal smear/culture
• Cryptococcal antigen
• Cytology
• Molecular diagnostics
# Typical CSF Findings

<table>
<thead>
<tr>
<th></th>
<th>WBC Count</th>
<th>Primary Cell</th>
<th>Glucose</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0-5</td>
<td>Mononuclear</td>
<td>40-80</td>
<td>15-50</td>
</tr>
<tr>
<td>Bacterial</td>
<td>1000-5000</td>
<td>Neutrophils</td>
<td>&lt;40</td>
<td>100-500</td>
</tr>
<tr>
<td>Viral</td>
<td>50-1000</td>
<td>Mononuclear</td>
<td>&gt;40</td>
<td>50-200</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>50-300</td>
<td>Mononuclear</td>
<td>&lt;50</td>
<td>50-300</td>
</tr>
<tr>
<td>Fungal</td>
<td>20-500</td>
<td>Mononuclear</td>
<td>&lt;50</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

**Exceptions:**

1. Very early meningitis: Can be normal
2. *Listeria monocytogenes*: Can be mononuclear-dominant
3. Early viral and tuberculous: Can be neutrophil-dominant
Typical CSF Appearance of Bacterial Meningitis

Normal CSF  CSF of Bacterial Meningitis  Gram Stain

Evaluation of Acute Meningitis

Neuroimaging (CT and MRI)

- **Computed Tomography (CT)**
  - “Quick evaluation” of intracranial process
  - Very good for bleeding and bony abnormality (e.g. skull base fracture)
  - Lower resolution of image
  - Can provide adequate information for the safety of LP

- **Magnetic Resonance Imaging (MRI)**
  - Longer time for study/care interruption
  - Low yield for meningeal process
  - Generally not necessary for the evaluation of acute meningitis
  - Should be obtained if there is any focal neurologic sign
Lumbar Puncture

When to Obtain CT Scan Before Procedure?

• **Possible Intracranial Mass**
  – Any focal neurologic sign
  – Any known intracranial pathology
  – Immunocompromised host

• **Possible Elevated ICP**
  – Presence of papilledema

• **Both**
  – Altered mental status

Attempts to safely perform lumbar puncture procedure should NEVER delay the administration of antibiotics for possible bacterial meningitis!!!

Suspected Acute Bacterial Meningitis

Suggested Sequence of Event in ER

**Points:**

1. If LP cannot be performed promptly, start empiric therapy immediately!!
2. **Goal of door-to-antibiotics time: <30 min**
“Couldn’t Get LP Done in ER…”

- **Presence of Contraindication**
  - Neurosurgical consultation
    - External ventriculostomy
- **Technical Difficulty**
  - Consultation to procedural experts (neurosurgery, interventional radiology, neurology)
- **Empiric antibiotics should be continued while waiting for CSF sampling**
  - Diagnostic yield of CSF culture can decline
    - Especially for *S. pneumoniae* and *N. meningitidis*
  - CSF analysis findings remain similar for 48-72 hours
  - Obtain blood cultures before starting empiric antibiotics
Newer Molecular Diagnostics

- **Multiplex PCR for CNS Pathogens**
  - Can test multiple pathogens simultaneously
    - Theoretically can detect even dead pathogens (i.e. after antibiotics administration)
  - Commercially available PCR kit
    - FilmArray™ (Biofire Diagnostics; FDA approved in 2015)
    - SeptiFast™ (Roche Diagnostics; off-label use)
    - Seeplex™ (Seegene; FDA approval pending)
  - In-house developed/validated tests at reference laboratory
Examples of Panel Contents

FilmArray™ Meningitis Panel (Biofire Diagnostics)

• Bacteria
  – Streptococcus pneumoniae
  – Neisseria meningitidis
  – Haemophilus influenzae
  – Listeria monocytogenes
  – Streptococcus agalactiae
  – Escherichia coli K1

• Virus
  – Cytomegalovirus (CMV)
  – Enterovirus
  – Herpes simplex virus 1 (HSV-1)
  – Herpes simplex virus 2 (HSV-2)
  – Human herpesvirus 6 (HHV-6)
  – Human parechovirus
  – Varicella zoster virus (VZV)

• Yeast
  – Cryptococcus neoformans/gattii

Not including: Klebsiella pneumoniae, arboviruses, tuberculosis

Turnaround Time: <2 hours

http://www.biofiredx.com/products/the-filarray-panels/
Is Multiplex PCR Game Changer?

Multicenter Validation Study for FilmArray™ ME Panel

• Prospective validation study at 11 referral academic centers in US
  – Enrolled 1560 CSF specimens
  – Compared to culture
    • Sensitivity: 93.9%; Specificity: 97.1%
    • PPV: 68.4%; NPV: 99.6%
  – Compared to cx + additional tests
    • Sensitivity: 95.8%; Specificity: 99.6%
    • PPV: 83.8%; NPV: 98.5%

Is Multiplex PCR Game Changer?

**Important Limitations**

- For relatively rare diseases (e.g. CNS infection), PPV still can be limited even with excellent sensitivity and specificity
  - "Premature closure" of the case can lead to delayed diagnosis
- Cannot provide antimicrobial susceptibility data
- Cost is still high

*Should not be considered as “replacement” for CSF culture*

Is Multiplex PCR Game Changer?

**Where Can This Technology Fit?**

**Multiplex PCR can:**
- Detect most common pathogens for CNS infections in timely manner
- Be useful at facilities without 24/7 microbiology specimen handling capability
  - CSF Gram stain examination requires microbiology technician with experience
  - Operation of multiplex PCR is very simple and requires minimal training
  - Limited value for hospitals with 24/7 microbiology lab

**Multiplex PCR should:**
- Be interpreted with appropriate clinical judgment
  - Aware for possible false-positive
  - Not all pathogens are included
- Not be considered as replacement for CSF culture

Jury is still out...
Take Home Points

• When CNS infection is suspected, acute evaluation should aim to exclude bacterial meningitis.

• Microbiology is highly variable to treat patient appropriately.
  – Successful vaccination has changed epidemiology significantly.
  – Pneumococcus is the most common cause of bacterial meningitis in US.
  – Consider patient risks (e.g. age, immune suppression) and environmental factors (e.g. season, travel).

• Newer molecular diagnostics are promising, but should be used with caution.
  – The result needs to be interpreted in clinical context.
  – “Premature closure” of the case can lead to mismanagement.
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QUESTIONS?