Fungal Meningitis: A Lesson in Preparing for the Unexpected

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Benefits of PHL Preparedness

- An intentional attack with a biological agent
- Outbreaks
  - Known endemic disease
  - New or remerging infectious disease
- Establish and maintain partnerships to leverage resources
The Laboratory Response Network

- Clinical/hospital
- Public health (OCME)
- Military
- Veterinary
- Agriculture
- Food
- Environmental
Virginia: 17 neuroinvasive cases, 9 non-neuroinvasive cases, 2 asymptomatic blood donors, and 3 fatalities. Highest numbers since 2003.
Rapidly Fatal Meningitis

09-12-12
Severe headache, Photophobia, Neck pain (cervical disk disease), Nausea, No fever or respiratory symptoms

09-06-12
ESI for Cervical Radicular Pain

09-16-12
Glucose 88
Protein 88
WBC 2300
RBC 50
MRI = meningitis

09-17-12
Intubated
Unresponsive Seizures

09-18-12
Death

09-20-12
WNV IgG Positive

Table 1. Typical CSF Findings in Patients With and Without Meningitis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Fungal Meningitis</th>
<th>Tuberculous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure (mm H2O)</td>
<td>&lt;180</td>
<td>200-500</td>
<td>NA</td>
<td>&gt;250 (Cryptococcus sp)</td>
<td>NA</td>
</tr>
<tr>
<td>WBC count (mm³)</td>
<td>0-5</td>
<td>100-20,000 (mean 800)</td>
<td>5-500 (mean 80)</td>
<td>20-2,000 (mean 100)</td>
<td>5-2,000 (mean 200)</td>
</tr>
<tr>
<td>WBC differential</td>
<td>No predominance</td>
<td>&gt;80% PMN</td>
<td>&gt;50% L, &lt;20% PMN</td>
<td>&gt;50% L</td>
<td>&gt;80% L</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>15-50</td>
<td>100-500</td>
<td>30-150</td>
<td>40-150</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>45-100 (2/3 of serum)</td>
<td>≤40 (&lt;40% of serum)</td>
<td>30-70</td>
<td>30-70</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Gram stain (% +)</td>
<td>NA</td>
<td>60-90</td>
<td>–</td>
<td>–</td>
<td>37-87 (AFB)</td>
</tr>
</tbody>
</table>

*: positive; –: negative; AFB: acid-fast bacilli; CSF: cerebrospinal fluid; L: lymphocytes; NA: not applicable; PMN: polymorphonuclear white blood cells. Source: References 9, 10.
Post-Mortem Analysis

- **R/O West Nile Virus Encephalitis**
- **OCME Specimen Collection**
  - Neural tissue (formalin fixed, fresh frozen, room temp)
    - Cultures initiated at DCLS
      - Viral cultures negative
      - Bacterial cultures positive for *P. acnes*
    - Tissues sent to CDC Infectious Disease Pathology Branch
  - Hospital laboratory all remaining specimens and culture plates
    - Serum: WNV IgM Neg, WNV IgG Pos
    - CSF culture had black mold (environmental contaminant)
- **Neuropathological findings suggestive of stroke**
- **Initiation of culture at the local level provided the only fungal isolate in this investigation**
Call for Cases: Meningitis Following Epidural Injections — Tennessee, 2012

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Brief Summary of Report:
Please report suspected cases of clinical meningitis/other neurologic infection with onset within 1 month of epidural injection since July 1 to Marion Kainer - 615-741-7247 or marion.kainer@tn.gov.

Description:
On 9/18/2012, the Tennessee Department of Health was notified of a patient with culture-confirmed Aspergillus fumigatus menigitis following epidural steroid injection (ESI) at a TN ambulatory surgical center.

Six additional patients with clinically-diagnosed meningitis were identified.

Symptoms of meningitis, including headache, stiff neck, and fatigue, developed within 1-4 weeks post-injection.

Two patients presented with additional local neurological deficits (strokes).

All had a similar cerebrospinal fluid (CSF) profile (low glucose, elevated protein and high, neutrophil-predominant, white cell count). CSF cultures on the 6 subsequent patients are negative to date.

Patients have generally received antibacterial antibiotics without improvement.

All patients received one or more ESIs during 7/30 to 9/18/2012.

All patients received injections of preservative-free methylprednisolone, preservative free normal saline, lidocaine, and skin prep with povidone-iodine.

Six of the patients received injections of omnipaque, a contrast material.

To understand the scope of this cluster and identify possible etiologies, we are seeking information on patients with clinical meningitis or possible neurologic infection (epidural abscess, spinal osteomyelitis, etc.), following epidural injections since July 1.

An epidemiological study is ongoing in collaboration with the ambulatory surgical center, state and federal public health partners.

Because Aspergillus meningitis can be difficult to diagnose, clinicians should consider this diagnosis in any patient presenting with similar signs and symptoms of neurologic infection post-ESI.

Diagnosis of Aspergillus meningitis should be sought by evaluating CSF for Aspergillus (galactomannan) antigen; fungal cultures of CSF should also be sent, preferably following centrifugation concentration. Do not discard any remaining CSF.

Empiric treatment with amphotericin B or voriconazole should be considered if Aspergillus meningitis is suspected.

State and local health departments are asked to disseminate this advisory widely to appropriate clinicians in their respective jurisdictions.

Public health officials who learn of suspected cases of clinical meningitis or other neurologic infection (i.e. epidural abscess, spinal osteomyelitis, etc.) with symptom onset within 1 month of epidural injection since July 1. are asked to contact Dr. Marion Kainer on 615-741-7247 or marion.kainer@tn.gov.

Unknown - Insufficient Data

Infectious Disease

Human

Actual
Total III or Injured: 7
Hospitalized: 7
Fungal Infections
Signs and Symptoms

- Fever
- New or worsening headache
- Stiff neck
- Nausea and vomiting
- Photophobia
- Altered mental status
- New weakness or numbness in any part of the your body
- Increased pain, redness or swelling at your injection site
- “Black mold”
Aspergillus Vs “The Unknown”

Aspergillus

VA Isolate
Aspergillus Vs Exserohilum

Aspergillus

VA Isolate

Exserohilum
Rapidly Fatal Meningitis

- **IDPB-CDC Report**
  - Polyfungal immunohistochemistry **Positive**
  - Immunohistochemical staining for *Aspergillus sp.* **Negative**
  - Molecular evidence of *P. acnes*

- **CDC Mycology Branch**
  - Preparedness training to SPHLs
  - PCR and sequencing of ribosomal DNA ITS-2 regions
    - Neural tissue **Positive**
    - CSF **Negative**
  - *Exserohilum rostratum* identified

- **Final Diagnosis:** *E. rostratum* meningitis
Case Definitions

- Fungal meningitis of sub-acute onset following ESI after May 21, 2012
- Posterior circulation stroke following ESI after May 21, 2012
- Evidence of spinal osteomyelitis or epidural abscess at the site of injection
- Septic arthritis or osteomyelitis of a peripheral joint following SI
Clinical Lab Guidance

- Use case definitions
- Collect \( \geq 5 \text{ml} \) CSF and 2 – 3 ml serum from meningitis cases
- Testing
  - CSF analysis (Cell CT/Dif, Glu, Protein)
  - Perform Gram stain, bacterial and fungal cultures, and AFB smears
  - Hold cultures for 4 weeks to enhance recovery of fungal agents
  - Send CSF and serum for *Aspergillus* galactomannan analysis
Shifting Mindsets

- Culture Isolates
  - *Aspergillus fumigatus* (TENN)
  - *Exserohilum rostratum*
  - *Propionibacterium acnes*

- Encourage an open mindset
NECC Preservative-free Methylprednisolone vials

- FDA and CDC analysis
- *Exserohilum rostratum* (lots 5, 6, and 8)
  - Predominant organism from clinical specimens and vials of MPA
  - Environmental mold
  - Rare cases of clinical illness
  - No reported cases of infection of central nervous system

*Exserohilum rostratum*
NECC MPA Healthcare Facilities

23 states, 76 facilities, and 17,675 vials
Clinical Challenges

- Patient notifications resulted in hundreds of patients seeking medical care in Virginia
- Many physicians had never seen or treated fungal meningitis
- Often difficult for patients to distinguish new symptoms from baseline symptoms
- Diagnostic test not without risk
Support Services

- Weekly patient evaluations with LP
- Specimens with a WBC >5
- Complete all necessary paperwork for CDC submission
- Quickly identified the need for data management and unique specimen id to determine date of collection
- Specimen storage
- Specimen tracking
- Spreadsheet-based reporting
- Verbal reports on positives
- Laboratory reports as they evolved
*n=814 case definition diagnoses among 702 cases
## Case-patient characteristics (n=696)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63</td>
<td>(16-97)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>415</td>
<td>(59)</td>
</tr>
<tr>
<td>Median no. injections (range)</td>
<td>1</td>
<td>(1-6)</td>
</tr>
<tr>
<td>MPA lot exposure known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lot 5</td>
<td>70</td>
<td>(10)</td>
</tr>
<tr>
<td>Lot 6</td>
<td>417</td>
<td>(59)</td>
</tr>
<tr>
<td>Lot 8</td>
<td>91</td>
<td>(13)</td>
</tr>
</tbody>
</table>
# Case-patient Laboratory Results

<table>
<thead>
<tr>
<th>Result</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-patients with specimens at CDC</td>
<td>495 (67)</td>
</tr>
<tr>
<td>Positive result</td>
<td>167 (34)</td>
</tr>
<tr>
<td><em>Exserohilum</em> sp.</td>
<td>148 (89)</td>
</tr>
<tr>
<td><em>Cladosporium</em> sp.</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Other fungi</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Laboratory-confirmed outside CDC</td>
<td>31 (4)</td>
</tr>
<tr>
<td>All laboratory-confirmed case-patients</td>
<td>198 (27)</td>
</tr>
</tbody>
</table>
NECC MPA Healthcare Facilities

23 states, 76 facilities, and 17,675 vials
Compounding Pharmacies

- Prepare customized medications that are not commercially available (prescription required)
- Regulated by the state boards of pharmacy
- Exempt from good manufacturing practice
- Products are not evaluated for clinical safety and efficacy
Outbreaks Linked to Compounding Pharmacies 2000 – Present (U.S.)

- **2001**
  - S. marcescens meningitis, joint infections, methylprednisolone (N=11)
  - Chryseomonas meningitis, methylprednisolone (N=2)

- **2002**
  - E. dermatitidis meningitis, joint infections, methylprednisolone (N=5)

- **2004**
  - P. fluorescens BSIs, heparinized saline flush (N=80)
  - B. cepacia BSIs, antibiotic flush (N=2)

- **2005**
  - S. marcescens BSIs, magnesium sulfate (N=18)
  - Various GNB, SIRS, cardoplegia (N=11)
  - P. aeruginosa, B. cepacia endophthalmitis, trypan blue (N=6)

- **2007**
  - S. paucimobilis BSIs, fentanyl (N=8)

- **2009**
  - Alpha-hemolytic Streptococcus endophthalmitis, bevacizumab (N=9)
  - S. marcescens BSIs, TPN (N=19)
  - S. mitis/oralis endophthalmitis, bevacizumab (N=12)

- **2011**
  - F. incarnatum, B. hawaiinesis endophthalmitis, BBG, triamcinolone (N=43)
  - E. rostratum, A. fumigatus meningitis, epidural abscesses, joint infections, multiple products (N>700)
  - E. dermatitidis meningitis, methylprednisolone (N=5)

- **2012**
  - Chryseomonas meningitis, methylprednisolone (N=2)

**Key:**
- BBG: Brilliant Blue-G; BSI: Bloodstream infection; GNB: Gram negative bacteria; SIRS: Systemic Inflammatory Response Syndrome; TPN: Total parenteral nutrition
NECC

- Recalled more than 2,000 products in addition to MPA and ceased operations in October 2012
- Filed for Chapter 11 bankruptcy in Dec. 2012
- Multitude of bacterial and fungal organisms were isolated from NECC products labeled as sterile
- Highlighted regulatory questions for compounding pharmacies
Summary

- Collaboration among multiple laboratories facilitated a rapid and effective response
  - Initiation of culture at the clinical lab
  - CDC Mycology Branch Training
- *Exserohilum rostratum* was identified in the patients and in the MPA compounded at the NECC
- Largest outbreak of healthcare associated infections in the US
- Patients are still at risk and cases continue to be reported
Acknowledgements

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  - Administrative support staff

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  - Willie Andrews

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  - Dr. Sherif Zaki

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  - Jo Ann Jellison
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CDC Recognizes Virginia Contribution

Dr. Tom Frieden @DrFriedenCDC
Kudos to VA state PH lab for 1st identifying Exserohilum, a black mold/fungus, in current meningitis outbreak. go.usa.gov/Ykb9
Retweeted by CDC_eHealth
Expand
Facility Locations Virginia

- >130 sentinel labs ⬤ ⭐
- 4 ME District Offices ★
- Emergency courier

Legend
- Sentinel Labs

DCLS

OCME
Rapidly Fatal Meningitis

- **CSF Bac Ag Panel**
  - Lyme
  - *H. influenzae*
  - S. pneumoniae
  - Grp B Strep
  - *Cryptococcus*

- **Culture**
  - CSF – NSG after 3 days
  - HSV and VZV
Suspect Case

- A person who has developed an infection of a normally sterile site following use of a product labeled as sterile prepared by the NECC