Fungal Infections Related to Contaminated Steroid Injections

September 26, 2013

Anurag Malani, M.D.
Medical Director, Infection Prevention and Antimicrobial Stewardship Programs
St. Joseph Mercy Health System
Adjunct Assistant Professor, University of Michigan

Disclosures

None

Background

- Sept 18, Index case - Aspergillus meningitis
- Sept 26, NECC recalled 3 lots of MPA
  - # 05212012@68
  - # 06292012@26
  - # 08102012@51
- 17,500 vials recalled - 75 facilities & 23 states
- Sept 27, Investigation by TN DOH, CDC, and NC DOH identified 8 additional pts with culture negative meningitis


By Oct 3, 6 cases of culture negative meningitis had been identified at SJMH
Oct 4, CDC Health Advisory warning of meningitis and stroke associated with MPA
Public health outreach by MDCH, SJMH, and independent pain facility

Types of Epidural Steroid Injections

- October (wks 1 – 3): mostly meningitis
- Incubation period: 1 – 4 wks after last injection (range 7 – 58 D)
- Symptoms: headache, meningeal sx, back pain, neck pain, + fever
- Laboratory: CSF WBC: < 10 WBC to 15K; at times neutrophil predominant, often low glucose, elevated protein

Clinical Presentations
Clinical Presentations

- Oct, 12 – May, 13: Spinal and paraspinal infections (including those with meningitis)
- Incubation period: Median of 56 days after last injection (Range 21 – 229 D)
- Symptoms: Back/neck pain (at injection site), headache, limb weakness/numbness
- Some patients with minimal symptoms
- MRI screening from Nov, 12 – April, 13

Clinical Presentation: Arachnoiditis

- Pain at the injection site
- Perineal and buttock pain/numbness
- Cauda equina syndrome: urinary retention, incontinence, leg weakness/numbness
- MRI: intradural clumping of nerve roots, operative intervention: + pus

Spinal and Paraspinal Infections

- Intradural abscess
- Epidural abscess
- Paraspinal abscess
- Osteomyelitis
- Discitis
- Facet joint infection

MRI Screening for Spinal & Paraspinal Infections

- MRI: intradural clumping of nerve roots, operative intervention: + pus

Monthly Admissions for Fungal Infections Related to Contaminated MPA

- September, October 2013
- November, December 2013

St. Joseph Mercy Ann Arbor - Fungal Infection Cases
Clinical Summary

195 Cases
- 54 Meningitis
- 128 Spinal / Paraspinal
- 13 Peripheral Joints
- 42 Spinal / Paraspinal

Microbiology

- 65 positive (of 195) for fungus
  - Predominantly - Exserohilum
  - PCR (CSF/tissue/Peripheral joint)
  - Culture (CSF/tissue/SJ joints)
  - Immunohistochemistry

Exserohilum rostratum

- Dematiaceous or black mold
- Melanin in its cell wall
- Found in the environment, plant debris, soil, and water
- Human infection uncommon
- Rarely, caused invasive infection in immunocompromised hosts

Diagnostic Testing

- Rapid development of fungal PCR test
- Diagnostic sensitivity
  - PCR: 29%
  - Culture: 14%
  - Combined PCR + culture: 33%
- PCR more sensitive than culture
- Molecular detection can accelerate diagnosis and treatment

Results of Molecular Testing

<table>
<thead>
<tr>
<th>Test Type</th>
<th>No. tested</th>
<th>No. positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All case patients</td>
<td>413</td>
<td>115 (28)</td>
</tr>
<tr>
<td>CSF</td>
<td>345</td>
<td>83 (24)</td>
</tr>
<tr>
<td>Synovial fluids</td>
<td>15</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Abscess aspirates</td>
<td>6</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Tissues</td>
<td>71</td>
<td>27 (38)</td>
</tr>
<tr>
<td>All samples</td>
<td>627</td>
<td>124 (20)</td>
</tr>
<tr>
<td>CSF</td>
<td>506</td>
<td>91 (18)</td>
</tr>
<tr>
<td>Synovial fluids</td>
<td>18</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Abscess aspirates</td>
<td>7</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Tissues</td>
<td>96</td>
<td>28 (29)</td>
</tr>
</tbody>
</table>

Therapy

- Backbones of treatment
  - Voriconazole (6 mg/kg q12)
  - Liposomal amphotericin B (5 mg/kg)
- Most patients given combination therapy
- Duration varied on disease presentation

Voriconazole

- Hallucinations, photopsia, QT prolongation, LFT abnormalities, drug interactions, photosensitivity
- CNS effects common, “trouble thinking”
- Prolonged treatment: alopecia, periostitis
- Monitoring: Troughs ranges < 1 to 16 ug/mL
- A/E profile shifted many pts to itraconazole

Voriconazole-Induced Photosensitivity

Voriconazole-Induced Alopecia

Liposomal Amphotericin B

- Drug infusion rxns
- Renal toxicity
- Electrolyte abnormalities – significant hypokalemia, hypomagnesemia
- Significant weight gain/edema with aggressive IV hydration, at times resulted in heart failure

Antifungal Susceptibility Testing of Exserohilum rostratum

<table>
<thead>
<tr>
<th>Antifungal agent (no. of isolates)</th>
<th>MIC (ug/ml)</th>
<th>MIC (ug/ml)</th>
<th>Mode (most frequent value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole (50)</td>
<td>1-4</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td>Fluconazole (50)</td>
<td>16-256</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Itraconazole (50)</td>
<td>0.25-4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Posaconazole (40)</td>
<td>0.25-1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Isavuconazole (50)</td>
<td>2-4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Amphoterocin B (44)</td>
<td>0.032-2</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The clinical relevance of MIC testing of this fungal pathogen remains uncertain, and breakpoints with proven relevance have yet to be identified or approved by CLSI or any regulatory agency.

http://www.cdc.gov/hai/outbreaks/laboratory/lab_testing_results.html
Costs of Anti-Fungal Therapy
- Anti-fungal budget from Oct, 12 – July, 13
  - Inpatient: $1.74 Million
    - Voriconazole: $500/day
    - Liposomal amphotericin: $400/day
  - Outpatient: $1.62 Million
    - Monthly voriconazole costs: $3000 – 7000

Case 1: Meningitis + Arachnoiditis
- **Chief complaint:** 72 y/o F with 1 wk of headache, neck stiffness, chills, and fatigue on 10/5/12
- **Epidural steroid injection:** L3-L4 on 9/20
- **Lumbar puncture:**
  - WBC: 549 cells/µl
  - Glucose: 45 mg/100mL
  - PCR: negative for fungal DNA
  - Protein: 53 mg/100mL
- **Medical treatment:**
  - Inpatient: voriconazole + L-AMB for 5 D
  - Discharge: 10/16 (26 D after ESI)
    - Symptoms: Improved
    - Outpatient treatment: oral voriconazole

Case 1: MRI 36 Days after Injection
- **Imaging:**
  - MRI: Enhancement projecting intradural at L3 level
- **Operative treatment:**
  - Evacuation of epidural abscess, L3 laminectomy
  - Intraoperative findings:
    - Phlegmon-like material adherent to clumping nerve roots
    - Small amount of pus, necrotic debris

Case 1: Operative Findings
- Phlegmon covering thecal sac
Case 1: Operative Pathology of Intradural Abscess

- Stain: H+E
- Findings: purulent inflammation
- Stain: GMS
- Findings: fungal hyphae

Case 1: Meningitis + Arachnoiditis

Hospitalization 2

- Medical treatment:
  - Inpatient: voriconazole + L-AMB for 5 wks
  - Discharge: 11/30/12
    - Symptoms: improved
    - Outpatient treatment: oral voriconazole
  - Imaging: 3/18/13 (About 5 Mo. after surgery)
    - MRI: Post-surgical change at laminctomy site, no abnormal epidural or intrathecal enhancement

Case 1: Meningitis + Arachnoiditis

Development of rib pain after 3 Mo. of voriconazole

- Imaging:
  - CT scan: periosteal reaction along B/L R 5-7, L 6-7 ribs
  - Bone Scan: intense tracer uptake B/L R 5-7, L6-7 ribs
- Laboratory:
  - Fluoride level .39 mg/L (normal < .10 mg/L)
- Medical treatment:
  - Voriconazole dose reduced, trough decreased
  - Periostitis pain resolved
  - Repeat LP normal in April, 2013 (4 WBC)
  - Transitioned to itraconazole in May, 2013, symptom free

Case 1: MRI 2 Months after Surgery

No abnormal intrathecal or epidural enhancement

Case 1: Periostitis of the Ribs

Case 1: Therapeutic Drug Monitoring of Voriconazole
Case 2: Epidural Abscess

- **Chief complaint:** 47 y/o M with headache, confusion, malaise, neck pain and spasms increasing since ESI
- **Epidural steroid injection:** C6-C7 on 10/2/12
- **Lumbar puncture:**
  - 4 unremarkable studies, last 30 D after ESI
- **Imaging:**
  - MRI: 3 unremarkable cervical studies, last 31 D after ESI
  - 4th MRI 42 D after ESI showed epidural abscess/phlegmon

Case 2: MRI Post-Injection - T1 Weighted

Case 2: MRI Post-Injection - T2 Weighted

Case 2: Operative Pathology of Epidural Abscess

- **Stain:** H+E
- **Findings:** acute inflammation next to bone
- **Stain:** GMS
- **Findings:** rare fungal hyphae

Case 2: Epidural Abscess

- **Operative treatment:**
  - **Procedure:** evacuation of epidural abscess, C5-C7 laminectomy
  - **Intraoperative findings:** abscess and pus
- **Medical treatment:**
  - Inpatient: voriconazole + L-AMB for 10 D
  - **Discharge:** 11/28
    - **Symptoms:** improved
    - **Outpatient treatment:** oral voriconazole thru May, 2013
- **Imaging:** 4/22/13 (About 4 ½ Mo. after surgery)
  - MRI: Resolution of abscess, extensive post-operative enhancing tissue

Case 1: MRI 2 Months after Surgery

Resolution of C5-T1 epidural abscess/phlegmon, post-operative enhancement
Lessons Learned

- Largest healthcare associated outbreak
- Broad spectrum of clinical disease and pathology
- Meningitis evolving disease
  - High percentage of infection at injection site
  - CVA or arachnoiditis - greater severity of illness
- Spinal/paraspinal infections: at site of injection
  - No evidence of noncontiguous spread
  - Surgical intervention an important role
  - Low threshold for MRI imaging, even in those with minimal change in symptoms - "asymptomatic"

Optimal duration of therapy unclear
- Varies upon disease presentation
- A/E of voriconazole likely more prominent with higher dosing and closer monitoring
- Itraconazole better tolerated for most pts
- Development of a Fungal Registry and the Fungal Outbreak Clinic critical for our health system’s public health response
- Regular calls and communication with the CDC and MDCH essential for management

Emergency Operations at SJMH

Remaining Questions

- Entry of pathogen into the CNS?
- Injection practices - translaminar approach?
- Direct entry ?, contiguous spread across dura
- Why did localized infections present later?
- Incubation period for spinal/paraspinal disease?
- Role of surgical intervention?
- Utility of other azoles? for CNS infection?
- Use of Beta-D-glucan?

- State-level variation?
  - Differences in degree of contamination
  - Receipt dates and storage times of the lots
  - Injection practices
  - Use of imaging to screen for localized disease

- Multicenter longitudinal followup study started
