Multistate Outbreak of Fungal Infections associated with Contaminated Steroids 2012 – 2013

Lessons Learned

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Mycotic Diseases Branch
CDC
“... one of the most shocking outbreaks in the annals of American medicine.”

Lawrence Altman
New York Times
November 5, 2012

Acknowledgments

- Hundreds of employees at 23 state health departments
- 300+ CDC employees
- FDA and DHHS employees
- Experts in fungal infection
- Physicians and others responsible for patient care
Tennessee Department of Health called CDC to discuss a case reported by an astute physician

- Patient with *Aspergillus* meningitis
- Had received an epidural steroid injection for pain

Somewhat unusual case

- Meningitis due to molds are very rare
- Patient was not immunocompromised

Steroid was a **compounded medication**

- Concern for contamination
What is Pharmacy Compounding?

- Extemporaneous combining, mixing, or altering of drug ingredients:*  
  By a pharmacist  
  In response to a prescription  
  For an individual patient

- Traditional component of pharmacy practice
- Meets needs that cannot be met with commercially-manufactured products

*U.S. Food and Drug Administration:  
Compounding Has a Broad Scope

Non-sterile

Orals
Inhaled, nasal products
Topicals
Transdermals

Ophthalmic solutions
Irrigations

Sterile

Injectables
• Anesthesia
• Antibiotics
• Electrolytes
• Flushes
• Intraoculars
• Parenteral nutrition
• Steroids

Cardioplegia solutions
Dialysis solutions
Recent expansion in scope and nature of activities

- In 2012, 7500 U.S. pharmacies specializing in advanced compounding services*
  - ~3000 provide sterile compounding services

*International Academy of Compounding Pharmacists: [http://www.iacprx.org](http://www.iacprx.org)
CDC contacted by TN DOH about a single patient with culture-confirmed *Aspergillus* meningitis following epidural steroid injection at an ASC.
Further investigation by TN DOH identified 7 additional patients with meningitis from same ASC.
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Unusual clinical cluster:

- All characterized by subacute onset of meningitis with marked CSF pleocytosis
- 4 had posterior circulation strokes
- CSF cultures from additional patients all initially negative
Further investigation by TN DOH identified 7 additional patients with meningitis from same ASC.

**Common links:**

All had undergone epidural steroid injection

Methylprednisolone acetate (MPA) from New England Compounding Center (NECC)

Other common exposures included: contrast material, povidone-iodine, lidocaine, spinal needles, epidural tray kits.
Very Unusual Cluster

- Immediate concern for some type of contamination
- Two main types of contamination
  - Extrinsic
    - Packaging
    - Surgical site
    - Air (HVAC, nearby construction)
  - Intrinsic
    - Medication itself
Prior Fungal Meningitis Outbreaks

- Surprisingly, there have been a few:
  - **Extrinsic contamination**
    - Sri Lanka following 2005 Indian Ocean tsunami
    - Moldy closet led to *Aspergillus* meningitis in pregnant women undergoing spinal anesthesia
    - Case fatality 60%
  - **Intrinsic contamination**
    - 2002 outbreak in NC of 5 cases of *Exophiala* meningitis
    - Compounded steroid medication
    - Distributed locally
    - Case fatality 20%
Initial Hypotheses

Clinic-based contamination?
- No new construction
- No problems with HVAC
- No flooding
- No change in practices
- No clustering by physician
- Many common products

Product-based contamination?
- Many common products
- Most nationally distributed
- Immediate concern about compounded steroid
Timeline - Two Weeks

FDA notified about investigation

Call with NECC to discuss concerns re: steroid

NECC stated it had not received any reports of illnesses and no concerning results with sterility testing or environmental monitoring
Timeline - Two Weeks

NECC issued voluntary recall of 3 lots of MPA used by the TN ASC

NECC provided list of all 76 facilities in 23 states that received recalled MPA to CDC

CDC used list to initiate case-finding in other states while also pursuing other possible sources of the outbreak
NC DOH identified patient with meningitis of unknown etiology following ESI at NC clinic

Suggested exposure may not be limited to TN ASC
Timeline - Two Weeks

Notification of patients exposed to recalled MPA initiated by health departments in collaboration with clinics

- Exposure still unknown
- Pathogen not identified except index case
Timeline - Two Weeks

FDA announced that unopened vials of MPA were found to be contaminated with fungus

Virginia state lab identified *Exserohilum* in deceased case

CDC activated Emergency Operations Center

CDC began direct patient notification of ~14,000 exposed persons
Major Outbreak Response

- Largest healthcare-associated outbreak reported in the United States

- Massive undertaking
  - Over 300 staff at CDC HQ
  - Thousands of staff nationally
    - State and local health departments
    - Clinicians, nurses, administrative staff

New York Times, October 8, 2012
The Concern

- Almost 14,000 persons exposed to contaminated MPA
- Delayed diagnosis in many patients → adverse events
- Of the initial 9 patients identified
  - 4 developed posterior circulation stroke
  - 3 died
- Limited experience with this type of infection
- Known outbreaks had 20-60% mortality
Public Health Actions: Major Components

- Patient Notification
- Clinical Guidance
- Laboratory Support
- Communications
Patient Notification

- Medication recalled on 9/26/12
  - Not enough
- CDC launched a collaborative effort to notify all exposed persons
  - Nature of the exposure
  - Indications to seek medical care
- Conducted mainly through clinic staff, state, local HDs
- The Goal: early diagnosis and treatment to reduce poor outcomes
- Within 10 days, >90% of all exposed persons were notified

CDC Emergency Operations Center
Engaged clinical expert mycologists with experience in fungal infections
- Best practices for diagnosis, treatment, and management
- Based on little to no data, but likely theoretical benefit

Resulted in real-time development, dissemination of recommendations for patient care
- Able to evolve with the rapidly changing outbreak
Laboratory Support

- Fungal diagnostics for CSF do not exist
- Novel PCR test developed in 2 days
- Quickly identified main fungus as *Exserohilum rostratum*
- >1,000 specimens processed during outbreak

OUTBREAK STATUS
Final Case Count reported on October 23, 2013

751 cases in 20 states
64 deaths
Sites of infection

- Meningitis
- Parameningeal infection
  - Epidural abscesses, vertebral osteomyelitis
- Peripheral joint infection
- Posterior circulation stroke in absence of CSF examination
  - Presumed to be due to undiagnosed meningitis
- 20% of patients have more than one site of infection
  - Most common: parameningeal disease and meningitis
Epidemic curve by diagnoses
Incubation period by diagnosis

Median incubation to first diagnosis: 47 days (0-249)
# National attack rates

<table>
<thead>
<tr>
<th>Injection type</th>
<th>Cases</th>
<th>Exposed</th>
<th>Attack rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All injections</td>
<td>751</td>
<td>13,534</td>
<td>5.5</td>
</tr>
<tr>
<td>Epidural/paraspinal injections</td>
<td>718</td>
<td>12,069</td>
<td>5.9</td>
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<tr>
<td>Peripheral joint injections</td>
<td>35</td>
<td>1,648</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Per 100 persons exposed
State-specific attack rates

States with exposures but no cases: CT, CA and NV
Did we achieve our goals?

- Early diagnosis
- Reduction in poor outcomes
Public health efforts reduced case-fatality

Responding to the Outbreak of Invasive Fungal Infections: The Value of Public Health to Americans
Beth P. Bell, MD, MPH; Rima F. Khabbaz, MD. JAMA. 2013;309(9):883-884.

Public health response saved >100 lives
Public health efforts led to early diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>On/before October 4</th>
<th>After October 4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>1,064</td>
<td>31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glucose</td>
<td>38</td>
<td>55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Protein</td>
<td>117</td>
<td>71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of symptoms</td>
<td>5</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antifungal treatment</td>
<td>58%</td>
<td>84%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>within 48 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LESSONS LEARNED
Detection of outbreaks

- Fungal diagnostics make identification difficult
- Wide distribution of contaminated products
  - Small clusters of disease across states, difficult to link together

Distribution of NECC MPA

Cases of MPA-associated illness
On October 6

- [http://www.cdc.gov/hai/outbreaks/meningitis-map.html#casecount_table](http://www.cdc.gov/hai/outbreaks/meningitis-map.html#casecount_table)
Patient notification

- Often difficult to identify who got a specific medication
  - Products from multiple manufacturers may be in use
  - Lot numbers may not be recorded
- Best way to notify patients
  - Letter
  - Phone calls
  - Home visits
- Risk communication strategies
  - Often before risk is fully realized
Identification of outbreak source

- Contaminated products may not be readily recognized as source of infection
- Compounding practices cannot always be observed, re-created
- Multiple infection control breaches can occur
  - Difficult to pinpoint exact source of contamination
- Unused product may not be available to test
  - Recovery of organisms may be difficult
Overall Keys to Success

- **Close collaboration among numerous partners**
  - Federal (FDA, CMS)
  - State
  - Local
  - Clinicians

- **Strong state health department public health infrastructure was essential**
  - Coordinate patient notification
  - Conduct case-finding, case reporting, and follow-up
  - Communicate changing clinical guidance
LOOKING FORWARD
Diagnostics

- **Beta-D-glucan (BDG)**
  - A cell wall polymer found in fungi
  - Available as commercial assay (Fungitell) for use in serum

- **CSF BDG is sensitive and specific**
  - For the diagnosis of *Exserohilum* meningitis
  - As a marker for treatment response

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Lyons JL et al., Cerebrospinal fluid (1,3)-B-D-Glucan detection as an aid for diagnosis of iatrogenic fungal meningitis. J Clin Microbiol 2013 (51)4:1285-7

Litvintseva et al., Utility of (1-3)-B-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. Clin Infect Dis 2013; first published online December 12, 2013 doi:10.1093/cid/cit808

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ROC curve for BDG cutoff values
Long term follow-up study

- Study to track long term outcomes of case-patients
  - Antifungal medications
  - Side effects
  - Outcomes including relapse, treatment failure
- CDC, UAB and Mycoses Study Group
- Enrollment, data collection is ongoing
  - Submission of latebreaker abstract to ICAAC 2014
Relapses?

- Five relapses have been reported to CDC
- All had received at least 3 months of antifungal therapy
- Most were complicated infections with arachnoiditis, toxicities
- 3 of 3 retrospectively tested had a CSF BDG identified as positive (>500 pg/mL)
  - BDG has promise for patient follow-up


Litvintseva et al., Utility of (1-3)-B-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. Clin Infect Dis 2013; first published online December 12, 2013 doi:10.1093/cid/cit808
What About Compounding?

- Outbreaks
- FDA, state enforcement actions (e.g., product recalls, license revocation)
- FDA “Warning Letters”
CDC investigations related to compounding pharmacies, 2001 - present

- 2001
  - *S. marcescens* in betamethasone
  - *P. fluorescens* in heparinized saline flush
  - *B. cepacia* in antibiotic flush

- 2002
  - *E. dermatitidis* in methylprednisolone

- 2004
  - *Chryseomonas* in methylprednisolone
  - *P. aeruginosa, B. cepacia* in trypan blue
  - *S. paucimobilis* in fentanyl

- 2005
  - *S. marcescens* in magnesium sulfate
  - Gram negative bacteria in cardioplegia solution

- 2007
  - *S. marcescens* in TPN
  - *S. mitis/oralis* in bevacizumab

- 2008
  - Alpha-hemolytic *Streptococcus* in bevacizumab

- 2009
  - *Neosartorya, Hamigera* in magnesium sulfate

- 2011
  - *F. incarnatum, B. hawaiinesis* in Brilliant blue-G dye, triamcinolone

- 2012
  - *E. rostratum* in methylprednisolone

- 2013
  - *Neosartorya, Hamigera* in magnesium sulfate
Attention Turned to Compounding Industry
Compounding Quality Act

- Signed into law as part of the Drug Quality and Security Act on November 27, 2013
- Amends the Federal Food, Drug, and Cosmetic Act (FDCA) in relation to human drug compounding
- **Section 503A**: “Traditional compounding”
  - Primarily regulated by states
- **Section 503B**:
  - Creates a new category of “registered outsourcing facility”
  - Pharmacies that register as an “outsourcing facility” will be primarily regulated by FDA
  - Will be inspected by FDA (risk-based schedule)
  - Subject to registration and re-inspection fees
  - Registration is **voluntary**
The Future?

- **Outbreak is over**
  - No new cases since summer 2013

- **Patients face tremendous anxiety**
  - CDC-INFO/phone duty inquiries
  - Infected and exposed

- **Starting to hear of more and more patients “cured”**

- **New legislation to expand FDA oversight may help**

- **Outbreaks will continue**
  - Strong public health system is essential
Thank You!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA  30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov   Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.