Large Fungal Outbreaks in the US: Role of the CDC Laboratory

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Outline

- Investigation of fungal meningitis and other infections caused by contaminated steroid
- Investigation of surgical site infections after cardiothoracic surgery
- Lessons learned
Role of the Public Health Lab
(in outbreak investigation)

- Collaborate with state and local Public Health Labs
  - Fungal identification

- Assist the Food and Drug Administration in linking pharmacy products to patient samples

- Conduct molecular typing to link cases of disease to particular sources

- Provide accurate and reliable information through CDC website and other media
Outbreak #1: The beginning…

- September 20, 2012
- Tennessee Department of Health called CDC
- Wanted to discuss an unusual case reported by an astute physician
  - Patient with *Aspergillus* meningitis
  - Had received an epidural steroid injection for pain July 30 at Clinic A
  - Somewhat unique infection
    - Meningitis due to molds are very rare
    - Concern for contamination somehow
    - Steroid was a compounded medication
The beginning continued…

- September 25, the TN DOH had identified 7 additional patients with meningitis from Clinic A

- Commonalities among patients
  - Injection at Clinic A
  - 1 of 3 lots of methylprednisolone acetate (MPA) from New England Compounding Center
  - Other possibilities – contrast material, povidone-iodine, lidocaine, spinal needles, epidural tray kits
NECC was contacted

- Notified of the investigation and involvement of lots of MPA
- Stated they had not been notified of adverse events and product passed sterility testing
- Instituted a voluntary recall of 3 lots of MPA
MPA distribution

- NECC provided a list of facilities that received MPA
  - 17,675 vials
  - 76 facilities
  - 23 states
  - ~13,000 individuals received injections
Index case was misleading

- TN index case had culture confirmed *Aspergillus fumigatus*
  - Isolated from both the CSF and the brain

- We began looking for cases of aspergillosis

- However, this was the only case of *Aspergillus* in the entire outbreak!
Cut to the chase…

- CDC opened Emergency Operations Center to assist states as necessary

- State and County public health divisions started contacting 14,000 potential patients

- Meanwhile, the Virginia SHD reported isolation of *Exserohilum rostratum* from brain tissue
Laboratory considerations

• We decided on broad range testing for all possible fungi
  ◦ Samples received were tissue and CSF
  ◦ All CSF pellets were negative for fungal DNA
  ◦ Decided to look for free DNA in CSF

• Used our experience with DNA extraction from paraffin blocks for tissue
Specimens

- 799 specimens or isolates from 469 case patients between 10/2012 and 2/2014
  - 547 CSF
  - 147 tissues
  - 67 isolates
  - 39 other body fluids (synovial fluid, epidural fluid)

Summary, patient specimens

- Patients with at least one specimen: 469
- Lab-confirmed Exserohilum patients: 150 (32%)
- Patients with other fungi: 19
  - Highlights:
    - Cladosporium cladosporioides (4 isolates, 1 by PCR)
    - Epicoccum sp. (1 by PCR)
    - Alternaria alternata (2 isolates)
    - Aspergillus fumigatus (TN index case)
MPA vial testing by FDA/CDC

- Lot 05212012@68 (produced May 2012): Paecilomyces formosus

- Lot 06292012@26 (produced June 2012): Exserohilum rostratum, Rhodotorula laryngis

- Lot 08102012@51 (produced August 2012): Exserohilum rostratum, Rhodotorula laryngis, Cladosporium cladosporioides, Rhizopus stolonifer, Bacillus sp (2 species)
Final patient tally

- 754 cases confirmed by isolate, fungal DNA detection or clinical findings
- 64 patient deaths
- Physicians were still reporting a few relapses two years out
Role of the Public Health Lab

- It was important in this outbreak to have a central reference location for specimen collection, molecular detection, and confirmation.

- Many states do not offer public health laboratory services in mycology.

- CDC relies on local expertise in detecting outbreaks:
  - A local clinician in TN reported the first cluster to the TN DOH.
  - The VA state laboratory reported the first isolation of *Exserohilum* to CDC.
    - The VA lab personnel had gained expertise through training in the CDC Mold Identification training course.
Role of local laboratories

- Local laboratories are critical in recognizing and reporting outbreaks.

- Unfortunately, proficiency in Medical Mycology is not a priority but was critical to this investigation.

- We estimate that prompt public health actions in this outbreak averted ~2900 contaminated injections and ~100-300 deaths.
Additional Take Home Messages

- Thinking outside the box is of value – tests in place are not always sufficient

- Be prepared for non-laboratory issues
  - Legal issues with data or specimens
  - Health alert system to rapidly disseminate information and results

- Least likely candidates can cause outbreaks in the right (or wrong) setting
Outbreak #2: The beginning…

- July, 2012
- Texas Department of State Health Services called CDC
- Discuss 4 cases of *Bipolaris* surgical site infections (SSI) in cardiothoracic surgery (CT) patients at Hospital A
  - Thought to be related to construction
  - Hospital performed remediation in 2012

Note: The *Bipolaris* species involved in this outbreak have been moved taxonomically to the genus *Curvularia*; the old name is kept here for historical purposes.
Outbreak #2: The beginning…

- November 22, 2013
- Texas Department of State Health Services again called CDC
  - Discuss 2 additional cases of *Bipolaris* SSI in CT surgery patients at Hospital A
  - Hospital B now reports 4 cases
  - Hospital B knew of an additional case at Hospital C in neighboring Arkansas
First Thoughts

- 11 cases, 3 hospitals, 2 states
- Same patient population

- Are we dealing with another contaminated product outbreak?

- Notice was sent out seeking additional cases of *Bipolaris* in CT patients
Initial Assessment

- Patients with *Bipolaris* were exclusively SSI in CT post-op patients
  - This became the case definition

- No SSI with other molds in CT patients

- No *Bipolaris* infections seen in patients who underwent other types of surgery
Hypotheses

- **Common medical device/product**
  - Topical agents used in chest
  - Compounding pharmacy products

- **Related to change in surgical practices**
  - SSIs are increasing in general and *Bipolaris* is being isolated because of general increase in SSIs.

- **Uncovering baseline rates of this infection**
  - It was there all along and we’re just now finding it

- **Environmental**
  - Fungal bloom of *Bipolaris* in the Southern US over recent years due to environmental changes
  - Construction activities at these hospitals
Hospital locations...

...Favor a commonality over environmental contamination
However…

- 3 additional CT patients with SSI due to *Curvularia*
- 3 additional patients with *Bipolaris*
  - 1 neurosurgery
  - 1 hemodyalysis patient with positive pericardial fluid
  - 1 bloodstream infection in a child on ExtraCorporeal Membrane Oxygenation
Overall increase in *Bipolaris* isolates

All *Bipolaris* Isolates from Hospitals in the area not Reporting Cases 2001 – 2013
Strain typing would be helpful

- No methodology existed for DNA typing of *Bipolaris*

- Could not even be sure if all the isolates were a single species

- No idea what the population structure of *Bipolaris* looks like

- Decided to use MultiLocus Sequence Typing (MLST) and looked for any *Bipolaris* genes present in NCBI Genbank
MLST plan devised

- 7 loci: \( \beta TUB, BRN1, GPDH, EF1\alpha, RPB1, RPB2, SAL1 \)
- Total coverage = ~3057 nucleotides

This MLST could type *B. spicifera, B. hawaiiensis, B. australiensis*, and *B. ellisii*
Phylogenetic tree of outbreak isolates based on MLST

B. spicifera

B. hawaiensis

B. australiensis
Hypothesis Check

- **Common medical device/product**
  - Ruled out – no complete commonalities

- **Related to change in surgical practices**
  - No increase seen in SSIs in any hospitals 2008-2013

- **Uncovering baseline rates of this infection**
  - An increase in *Bipolaris* all-site infections was seen so unlikely

- **Environmental**
  - Most likely
Take Home Messages

- Close collaboration between the epidemiology and laboratory teams helped to narrow the focus of the investigation.

- Outbreak investigations do not always lead to a crystal clear answer.
Final Thoughts

- Cooperation between public health and state and local officials is essential for outbreak investigation and data dissemination

- Every outbreak is different, one of the most important aspects of any investigation is preparedness

- Recently, Whole Genome Sequence typing has allowed us to both solve outbreaks as well as provide sequences for novel MLST schemes
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