Botulism: Clinical Aspects

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Jars of contaminated Jalapeño peppers involved in an outbreak of botulism in Pontiac, Michigan, April, 1977. (CDC-PHIL)
Botulism- Clinical Syndromes

I. Ingestion of toxin

- Wound
  - Contamination of wounds by soil
  - Improper fracture management
  - Black-tar heroin “skin-popping”
  - Cocaine- sinusitis

- Post-therapeutic/cosmetic

- Intentional (terrorism)
  - Inhalational
  - Foodborne
  - waterborne

- Inhalational
  - Laboratory workers

- Foodborne

- Waterborne*

*unlikely with water treatment processes
Botulism - Clinical Syndromes

II. Ingestion of spores

- Infant botulism
  - Ingestion of food (raw honey)
  - Ingestion of soils
- Adult (intestinal) botulism
  - Prior antimicrobial use
  - Altered anatomy
- Spores germinate in colon
Epidemiology

- Frequency: <200/yr US
- Incubation: 6h-10 days
  - Foodborne- 12-36 hours to several days
    - Shorter incubation-> higher case fatality
  - Infant/adult intestinal-variable
  - Inhalational- 12-80 hours
- Transmissibility: None known

Botulism Symptoms

Botulism Diagnosis

• Suspect in any adult with findings:
  – gastrointestinal (constipation, nausea, vomiting)
  – autonomic (e.g., dry mouth, difficulty focusing)
  – cranial nerve (diplopia, dysarthria, dysphagia)
• Suspect in any infant with:
  – poor feeding
  – diminished sucking and crying ability
  – neck and peripheral muscle weakness
  – and/or ventilatory distress.
**Differential Diagnosis**

- Guillain-Barre syndrome
- Myasthenia gravis
- Cerebrovascular accident (CVA)
- Bacterial and/or chemical food poisoning
- Tick paralysis
- Chemical intoxication (e.g., carbon monoxide)
- Mushroom poisoning
- Poliomyelitis
- Ingestion of marine biotoxins (e.g., paralytic shellfish poisoning)

Rapidly Exclude Botulism

Tests to Consider:
- Lumbar puncture
- CNS Imaging
- Tensilon test
- Tick inspection
- EMG
- Autoantibodies
- Stool culture
- Campylobacter

Botulism-Bioterror

- Most potent toxin known to man
- Pancho Villa- 1910
- WWII
- US and Soviet
  - Agent X
  - Aerosolization inferior to that of anthrax and tularemia
  - Relative instability
- Iraq-19,000L (UN)

Likely modes:
- Aerosol (enc. areas)
- Contamination of food

Box 1. Features of an Outbreak That Would Suggest a Deliberate Release of Botulinum Toxin

Outbreak of a large number of cases of acute flaccid paralysis with prominent bulbar palsy

Outbreak with an unusual botulinum toxin type (ie, type C, D, F, or G, or type E toxin not acquired from an aquatic food)

Outbreak with a common geographic factor among cases (eg, airport, work location) but without a common dietary exposure (ie, features suggestive of an aerosol attack)

Multiple simultaneous outbreaks with no common source

Note: A careful travel and activity history, as well as dietary history, should be taken in any suspected botulism outbreak. Patients should also be asked if they know of other persons with similar symptoms.

Public Health Response

• True public health emergency
• Support Clinical Management
  – Testing
  – Antitoxin or IG procurement
• Investigate to ascertain public health impact
  – Foodborne, post-therapeutic/cosmetic, or intentional:
    • Single or multiple cases?
    • Common exposure?
    • Implicated food?

Mitigate public health impact
Treatment

• Call your local public health department
• Local health department contacts state health department
• State health department consults CDC as indicated
• CDC will work with state health initially
• CDC: 800-CDC-INFO

• Supportive
• Antitoxin
  – Heptavalent now available (A-G)
  – DOD-developed
• Botulism Immune Globulin Intravenous (Human)
  • Infant botulism only
  • California Department of Public Health’s Infant Botulism Treatment and Prevention Program Berkeley, CA
Botulism-Prognosis

• The prognosis for case-patients who develop botulinic paralysis is good
  – if secondary complications are prevented
• The greatest improvement is in the first 3 months
• Patients can continue to improve for a year after exposure
• Most require rehabilitative therapy
Botulism: Laboratory Aspects

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Botulism toxins

- Seven antigenic types: A, B, C, D, E, F, G
  - Toxin types A, B, and E most commonly associated with human disease
- Toxin produced by *C. botulinum*
  - May be produced by *C. butyricum*, *C. argentinense*, *C. baratii*
- Strains generally only make one toxin
  - Strains may have genes to make more than one type
Botulism toxin

• Most toxic substance known
  – Estimated oral lethal dose: 0.2 – 1 µg/kg
  – Toxin is odorless, colorless, and tasteless

• Toxin secreted as a progenitor toxin
  – 150 kDa protein that must exposed to protease to cleave to active toxin. 100 kDa and 50 kDa proteins

• Type A most potent. Types B & E cause longest lasting disease
Specimen collection

- Serum
  - 10 - 15 ml. Store at 4-8°C.
- Stool
  - 15 – 25 g. No preservative. Store at 4-8°C.
- Food
  - 100 – 150 g. In original container.
  - Store under original conditions.
- Wounds
  - Anaerobic transport. Room temperature.
Testing methods

• Mouse bioassay
  – Gold standard
  – Limit of detection
• Dig-ELISA
  – Limit of detection
• PCR
Mouse Bioassay

- Serum tested without further processing
- Stool
  - Extract prepared for direct testing
  - Culture enrichment
- Food
  - Extract prepared for direct testing
  - Culture enrichment
## Mouse bioassay: serum

<table>
<thead>
<tr>
<th>Mouse pair</th>
<th>Volume serum</th>
<th>Volume antitoxin</th>
<th>Antitoxin type</th>
<th>Volume injected/mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 ml</td>
<td>0 ml</td>
<td>-</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>2</td>
<td>1.0 ml</td>
<td>0.25 ml</td>
<td>A</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>3</td>
<td>1.0 ml</td>
<td>0.25 ml</td>
<td>B</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>4</td>
<td>1.0 ml</td>
<td>0.25 ml</td>
<td>E</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>5</td>
<td>1.0 ml</td>
<td>0.25 ml</td>
<td>F</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>6</td>
<td>1.0 ml</td>
<td>0.25 ml</td>
<td>ABE</td>
<td>0.5 ml</td>
</tr>
</tbody>
</table>
# Mouse bioassay: stool, food, enrichment cultures

<table>
<thead>
<tr>
<th>Mouse pair</th>
<th>Specimen Volume</th>
<th>Treatment</th>
<th>Antitoxin Type</th>
<th>Volume injected/mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 ml</td>
<td>None</td>
<td>None</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>2</td>
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<td>Heat</td>
<td>None</td>
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</tr>
<tr>
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<td>Trypsin</td>
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</tr>
<tr>
<td>4</td>
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<td>0.25 ml antitoxin</td>
<td>A</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>5</td>
<td>1.0 ml</td>
<td>0.25 ml antitoxin</td>
<td>B</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>6</td>
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<td>0.25 ml antitoxin</td>
<td>E</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>7</td>
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<td>0.5 ml</td>
</tr>
<tr>
<td>8</td>
<td>1.0 ml</td>
<td>0.25 ml antitoxin</td>
<td>ABE</td>
<td>0.5 ml</td>
</tr>
</tbody>
</table>
**Dig-ELISA**

- Detects specific toxin
  - Cannot differentiate biologically active from inactivated toxin
  - May exhibit cross-reactivity between toxin types

- Application
  - Food (interference from some matrices)
  - Enrichment cultures
  - Limited information on serum and feces
PCR

- Detects *bot* gene
  - Testing complete in about 4 hours
  - Does not confirm gene expression
  - Does not differentiate living vs. dead organisms
  - Does not detect biologically active toxin
- Direct specimen testing
  - Potential inhibition
- Enrichment cultures
  - Food and environmental sources
Questions