Infant Botulism

Environmental Health – Food Protection Services

BC Centre for Disease Control
Topics

- History of Botulism
- Mode of Action
- Infant Botulism (Intestinal Botulism)
  - Symptoms & Diagnosis
  - Treatment - BabyBIG
  - Neurotoxin Types & Groups
  - Risk Factors
- Food Sources (honey)
- Laboratory Diagnosis
- References
Botulism – a short history

- Emperor Leo VI of Byzantium (886-911 A.D.) forbade his people to eat blood sausages.
- 1793, southern Germany, 6 of 13 died, initially diagnosed as belladonna poisoning. “Blunze” - pig stomach/blood preserved by smoking.
- 1820-22 in Germany Justinus Kerner collected data on 230 cases of sausage poisoning due to “corpse acid”.
- Recognized in Russia in 1818
  7 cases of paralytic illness in Yakutsk due to salted fish.
  Known as ichthyism!
- ~1900 Dr. van Ermengem isolated an anaerobic spore-forming bacillus from the spleen of a victim
  described this organism as *Bacillus botulinus*
1924 – Albany, Oregon

- Home-canned string beans
- All 12 people family members died
**C. botulinum**

- Gram positive
- Anaerobe
- Spore Former
- Oval subterminal endospores
- Motile

www.hpa.org CDC Public Images 2132, 1930
Botulism – what is the disease?

- Botulism causes an intoxication that damages the nerves.
- Ingestion of protein toxin blocks the release of acetylcholine at neuromuscular junctions.
- This stops muscle contractions and paralyzes skeletal muscle cells – “muscular paralysis”.
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ACh released, binding to receptors</td>
</tr>
<tr>
<td>2.</td>
<td>Action potential reaches T tubule</td>
</tr>
<tr>
<td>3.</td>
<td>Sarcoplasmic reticulum releases Ca^{2+}</td>
</tr>
<tr>
<td>4.</td>
<td>Active-site exposure, cross-bridge formation</td>
</tr>
<tr>
<td>5.</td>
<td>Contraction begins</td>
</tr>
<tr>
<td>6.</td>
<td>ACh removed by AChE</td>
</tr>
<tr>
<td>7.</td>
<td>Sarcoplasmic reticulum recaptures Ca^{2+}</td>
</tr>
<tr>
<td>8.</td>
<td>Active sites covered, no cross-bridge interaction</td>
</tr>
<tr>
<td>9.</td>
<td>Contraction ends</td>
</tr>
<tr>
<td>10.</td>
<td>Relaxation occurs, passive return to resting length</td>
</tr>
</tbody>
</table>
The Function of a Cholinergic Synapse

1. **Mitochondrion**
2. **Acetylcholine**
3. **Acetylcholinesterase**
4. **Acetyl-CoA**

**Steps:**
- **STEP 1:** An action potential arrives and depolarizes the synaptic knob.
- **STEP 2:** Extracellular Ca²⁺ enters the synaptic cleft triggering the exocytosis of ACh.
- **STEP 3:** ACh binds to receptors and depolarizes the postsynaptic membrane.
- **STEP 4:** ACh is removed by AChE (acetylcholinesterase).
**FIGURE 12–20**  
The Mechanism of Drug Action at a Cholinergic Synapse.  Factors that facilitate neural function and make neurons more excitable are shown in violet. Factors that inhibit or depress neural function are in blue.
Types of Botulism

- Food Botulism
- Wound Botulism
- Infant Botulism
- Child/Adult Botulism

Intestinal Botulism
Infant Botulism

- Affects children less than 12 months old
  - Median age: 10 wks (2 wks to 1 yr)
    - exception: 7.6 days for *C. baratti* (rapid progression)
- Ingestion of *C. botulinum* spores cause the illness (food or environmental)
  - *in situ* production of toxin by *Clostridium* bacteria, gut microflora fail to competitively inhibit outgrowth of spores
- Mild to severe illness
  - Feeding difficulties, mild hypotonia, floppy neck → respiratory failure, infant death
- Incubation period from 3 to 30 days after exposure
Symptoms & Diagnosis

- 1\textsuperscript{st} symptom constipation (95%)
- “Floppy baby”, listless, lethargic, poor head control
- Difficulty swallowing & sucking, weak cry
- Flaccid expression
- Pupils don’t react to light
- Weak gag reflex

Diagnosis:
- EMG – electromyogram
- Stool specimen
Treatments

- Supportive and respiratory care
- Nasogastric feeding, mechanical respiration
- BabyBIG
- Wait until recovery of nerve function: regeneration of terminal motor neurons
- Hospital stays from one month to a year
### Differences in Outcomes of Infants Treated with BIG-IV (BabyBIG)


#### Randomized Placebo-Controlled Trial (129 Infants)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>BIG-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Hospitalization</td>
<td>5.7 wk</td>
<td>2.6 wk</td>
</tr>
<tr>
<td>ICU care</td>
<td>5.0 wk</td>
<td>1.8 wk</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4.4 wk</td>
<td>1.8 wk</td>
</tr>
<tr>
<td>Tube feeding</td>
<td>10.0 wk</td>
<td>3.6 wk</td>
</tr>
<tr>
<td>Total hospital charges</td>
<td>$163,000</td>
<td>$74,800</td>
</tr>
</tbody>
</table>

#### Open-Label Use (366 infants)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BIG-IV @4-7 days hosp</th>
<th>BLV-IV@ &lt;4 days hosp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>2.9 wk</td>
<td>2.0 wk</td>
</tr>
</tbody>
</table>

All differences statistically significant p<0.001
Botulism neurotoxin types

- A, B, E, F affect humans
- $C_1$, $C_2$, D affect birds, mammals
- G not found to cause illness
- AB, BF dual toxin strains

(C. butyricum, C. baratii also known to produce type E & F toxins)
# Botulism Groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteolytic</strong></td>
<td>Proteolytic</td>
<td>Non-proteolytic</td>
<td>Non-proteolytic</td>
<td></td>
</tr>
<tr>
<td><strong>Neurotoxin</strong></td>
<td>A, B, F</td>
<td>B, E, F</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Optimal temp</strong></td>
<td>35-40°C</td>
<td>18-25°C</td>
<td>40°C</td>
<td>37°C</td>
</tr>
<tr>
<td><strong>Range temp</strong></td>
<td>10-48°C</td>
<td>3-45°C</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>survival (min/max)</strong></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>4.6</td>
<td>5.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Salt</strong></td>
<td>10%</td>
<td>5%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Aw</strong></td>
<td>0.94</td>
<td>0.97</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Spore Inactivation Step†</strong></td>
<td>25’ @ 100°C, 0.1-0.2’ @ 121°C</td>
<td>&lt;0.1’ @ 100°C, &lt;0.001’</td>
<td>&lt;0.1 to 0.9’ @ 100°C</td>
<td>&lt;0.8 to 1.1’ @ 100°C</td>
</tr>
</tbody>
</table>

†- Note: in commercial canning operations, a 12D (12 log reduction) process is typically 2.4 min at 121°C (250°F)
### Water Activities of various foods

<table>
<thead>
<tr>
<th>Food</th>
<th>$a_w$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh fruit, veg, meat, fish</td>
<td>&gt;0.98</td>
</tr>
<tr>
<td>Cooked meat, bread</td>
<td>0.98 - 0.95</td>
</tr>
<tr>
<td>Cured meat products, cheeses</td>
<td>0.95 - 0.91</td>
</tr>
<tr>
<td>Sausages, syrups</td>
<td>0.97 - 0.87</td>
</tr>
<tr>
<td>Flours, rice, beans</td>
<td>0.87 - 0.80</td>
</tr>
<tr>
<td>Jams, marmalades</td>
<td>0.80 - 0.75</td>
</tr>
<tr>
<td>Candies</td>
<td>0.75 - 0.65</td>
</tr>
<tr>
<td>Dried fruits</td>
<td>0.65 - 0.60</td>
</tr>
</tbody>
</table>
Minimal $a_w$ for growth of...

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>$a_w$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most bacteria</td>
<td>0.91 - 0.88</td>
</tr>
<tr>
<td>Most yeasts</td>
<td>0.88</td>
</tr>
<tr>
<td>“Regular molds”</td>
<td>0.80</td>
</tr>
<tr>
<td>Halophilic bacteria</td>
<td>0.75</td>
</tr>
<tr>
<td>Xerotolerant molds</td>
<td>0.71</td>
</tr>
<tr>
<td>Osmophilic yeasts</td>
<td>0.62 - 0.60</td>
</tr>
</tbody>
</table>
Processing of Foods for $a_w$
Processing of Foods for $a_w$

Chilled mirror dew-point technique

Photo: BC Centre for Disease Control
Adult classical Botulism: BC case
“Stink Eggs”
Type E Botulism

Photo: BC Centre for Disease Control
Infant Botulism Types & Risk Factors

- Type A is found in the west / Type B is found in the east

- Risk factors and predisposing conditions…
  - ingestion of honey – risk of Type B
  - parent has daily contact with soil / living on a farm / living in area following an earthquake
  - windy, high soil water and alkaline content
  - possible seasonal trend: cases between March and October (not winter)
  - exclusively breast-fed infants during weaning (change in gut microflora)
  - introduction of first formula feeding
  - age onset differences:
    - formula-fed: 7.6 weeks, breast-fed: 13.7 weeks (±8.4 weeks)
  - host factors role in pathogenesis
Spores found in....

- Honey
- Yard soil
- Vacuum cleaner dust
- Infant Formulas
Laboratory Investigation – Infant Botulism

- Specimen to be submitted: **stool**

  NOT blood or serum (rarely does toxin circulate in infant blood)
  - Exception: early in course of infection
Laboratory Methods

- **Mouse assay – intraperitoneal** Inject culture filtrates, food filtrates or serum into mice
- **Look for symptoms**
  - Wasp-like or constricted waist
  - Ruffled hair
  - Difficulty breathing, failure to right response
  - Death
- **TAT for mouse assay**
  - Serum: 48 hours minimum for negative result
    - If positive, signs may be observed within 4 to 8 hrs post-inoculation, usually 24 hrs is required.
  - Culture (stool, food): 5 to 7 days
Infant Formula Problems

- Botulinum Type B in Infant Powder Ireland 2001 (SMA nutrition: white infant formula)
- Thiamine Deficiency in Infant Formula, Israel, November 2003
- *Enterobacter sakazakii* in Powdered Infant Formulas, Canada, July 2002
- *Bacillus cereus* in Powdered Infant Formulas, Survey, Germany, 1994
BCCDC Contacts for Case Management and Investigations

- When botulism is suspected, immediately inform the local Medical Health Officer
- Contact the on-call Physician for BCCDC at 604.312.9222 regarding provision of botulism antitoxin
- Contact the on-call Medical Microbiologist at Laboratory Services (BCCDC) 604.661.7033 for consultation and approval of sample testing
- Phone Food Poisoning Laboratory (BCCDC) 604.707.2611 for priority sample submission information
- Phone Food Protection (BCCDC) 604.707.2440 for consultation regarding Food Recalls & investigation

BCCDC Reference Links:
1. Communicable Disease Control Chapter 1 - Botulism
2. PHSA Programs and Services
References

- Laboratory Services, BC Centre for Disease Control (photographs)