Infant Botulism: Epidemiology, Clinical Features and Treatment

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Disclosures

Ms. Payne has no relevant financial interests or commercial relationships to disclose.

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Objectives

At the conclusion of this presentation, participants will be able to:

• Describe the typical clinical features of infant botulism
• Identify key epidemiological features of infant botulism
• Understand basic laboratory aspects of infant botulism testing and specimen submission
• Describe the process for obtaining clinical consultation and Human Botulism Immune Globulin (BIG-IV or BabyBIG®) from the California Infant Botulism Treatment and Prevention Program (IBTPP)
Outline

• What is infant botulism?
• Epidemiology of infant botulism
  – Geographic distribution
  – Age distribution
  – Exposures
• Infant botulism testing
• Treatment of infant botulism and the IBTPP
What is infant botulism (IB)?

- Temporary intestinal colonization by *Clostridium botulinum*, spore-forming obligate anaerobe
- Affects infants less than 1 year of age
- A rare disease, but most common form of human botulism in the US for more than 30 years
- Symptoms include generalized muscle weakness, with airway and swallowing difficulties
  - Affected infants require hospitalization for feeding and breathing supportive care. Approximately ½ of patients need ventilator care in pediatric ICUs.
Pathophysiology

• Swallowed spores germinate, then temporarily colonize and produce botulinum neurotoxin (BoNT) in the large intestine

• BoNT is absorbed; carried by bloodstream

• BoNT binds to peripheral cholinergic nerve endings

• BoNT cleaves key intracellular proteins necessary for acetylcholine release resulting in flaccid paralysis

• BoNT does not cross blood-brain barrier
BoNT mechanism of action

Clinical insights

• IB presents as a descending, symmetrical, flaccid paralysis with bulbar palsies in previously well infants

• The clinical spectrum of IB ranges from very mild, outpatient cases to severe/fulminant/SIDS-like presentation*

• A complete recovery expected, in the absence of complications

• Treatment consists of meticulous supportive care (respiratory and feeding support) and antitoxin (BabyBIG®) administration


Presenting characteristics

Percent of infant botulism patients reported as presenting with these symptoms, California 1992 - 2017 (N=784)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized weakness</td>
<td>97%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased head control</td>
<td>96%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Poor suck</td>
<td>94%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>89%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>77%</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Sluggish pupils</td>
<td>49%</td>
<td>35%</td>
<td>16%</td>
</tr>
<tr>
<td>Respiratory difficulty</td>
<td>31%</td>
<td>67%</td>
<td>2%</td>
</tr>
<tr>
<td>Honey exposure</td>
<td>5%</td>
<td>93%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Epidemiology of infant botulism

• 3715 US lab-confirmed cases IB cases 1976-2017
• 49.6% Female, 50.3% Male, 0.1% Unknown
• Cases in all major racial and ethnic groups
• Occurrence in all 50 US states & Washington DC
• Caused by strains producing A, B, E, F, Ab, Ba and Bf botulinum toxins
Incidence of infant botulism per 100,000 live births, 1976 - 2016

US total = 2.2 / 100,000 live births

Top 5 states

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>California</td>
<td>Delaware</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>Utah</td>
</tr>
<tr>
<td>New Jersey</td>
<td>Hawaii</td>
</tr>
<tr>
<td>Texas</td>
<td>Pennsylvania</td>
</tr>
<tr>
<td>Utah</td>
<td>California</td>
</tr>
</tbody>
</table>

Arizona (rank 12) Arizona (rank 18)
US infant botulism cases, by toxin type, 1976-2017 (n = 3713)

Size of pie chart proportional to number of cases.

Legend
Toxin type
- A
- Ab
- B
- Ba
- Bf
- Br
- E
- F
Age distribution for California infant botulism patients, 1976 - 2017
n = 1389

- 0-6 mo
  - AUC = 88% of total AUC

- 7-12 mo
  - AUC = 12% of total AUC
Exposures

- *C. botulinum* is a soil-dwelling, spore-forming bacterium found in soils throughout the world
- Soil disturbance (e.g., construction) may make more spores available in the immediate environment
- Most patients likely acquire spores by swallowing microscopic dust particles on which the spores travel
- Honey is the one identified and avoidable food reservoir of *C. botulinum*, and is not a necessary food for infants
Infant botulism patients with honey exposure, California, 1976 - 2017

- Number of cases with honey exposure
- Percentage of cases with honey exposure

Graph showing the decrease in number of cases and percentage of cases with honey exposure from 1976-1979 to 2015-2017.
Infant botulism in Arizona

<table>
<thead>
<tr>
<th>County</th>
<th>A</th>
<th>B</th>
<th>E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>COCONINO</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>MARICopa</td>
<td>6</td>
<td>19</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>MOHAVE</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>PIMA</td>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>PINAL</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>26</td>
<td>1</td>
<td>38</td>
</tr>
</tbody>
</table>

AZ infant botulism cases by county, 2000-2018 (YTD)

US incidence of infant botulism per 100,000 live births, 1976 - 2016

<table>
<thead>
<tr>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>1-3.9</td>
</tr>
<tr>
<td>4-10</td>
</tr>
<tr>
<td>&gt;10</td>
</tr>
</tbody>
</table>
Arizona infant botulism cases, by toxin type, 1977-2018 (ytd)

- Toxin A
- Toxin B
- Toxin E

Yearly counts from 1977 to 2018 are displayed, showing the number of cases for each toxin type.
Infant botulism testing

• Botulism stool/enema testing required for all infants treated with the antitoxin BabyBIG®

• Specimens for AZ infants are sent through AZ DPH to CDC’s botulism diagnostic laboratory

• Case definition = detection of *C. botulinum* or BoNT in the feces or enema from a symptomatic infant

• Serum is not a reliable specimen for infant botulism testing

• Fecal specimens can be collected before or after antitoxin administration
Infant botulism testing, cont.

• The current “gold-standard” test for infant botulism is the mouse bioassay for detection of BoNT
• Specimens are also often cultured to isolate *C. botulinum*
• Molecular methods including PCR and mass spectrometry may also aid in the diagnosis
BabyBIG for the treatment of IB

- BabyBIG is a public-service, orphan drug available through consultation with IBTPP
- Human antitoxin/IgG
- In-vivo half-life of 28 d
- Protective for 5+ mo following single infusion
- Neutralizes circulating toxin; does not reverse existing paralysis; early treatment maximizes efficacy
- Enables more rapid recovery and thereby results in shorter length of hospital stay and reduced hospital costs*


BabyBIG efficacy

Reductions in Hospital Stay and Costs Achieved with BIG-IV (BabyBIG) Treatment of U.S. Infant Botulism Patients During its Pivotal Phase 3 Trial and, its 12 years Post-Licensure

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean Stay (wks)</th>
<th>Hospital Stay Avoided with BIG-IV Use</th>
<th>Mean Costs</th>
<th>Hospital Costs Avoided with BIG-IV Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (wks) Total (yrs)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group for phase 3 trial (CA)†</td>
<td>63</td>
<td>5.7</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Infant botulism patients treated with BIG-IV during the phase 3 trial (CA)</td>
<td>59</td>
<td>2.6</td>
<td>3.1</td>
<td>3.5</td>
<td>$95,200</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Infant botulism patients treated with BIG-IV in the first 12 years post-licensure (U.S.)</td>
<td>1133</td>
<td>2.2</td>
<td>3.6</td>
<td>66.9</td>
<td>$118,600</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1123</td>
<td>2.2</td>
<td>3.6</td>
<td>66.9</td>
<td>$118,600</td>
</tr>
</tbody>
</table>

* Treated in the U.S. within 7 days of hospital admission. Only patients with type A or B illness included.
† Reference group comprised of pivotal clinical trial placebo-treated patients 1992-97. Length of stay numbers rounded to the nearest tenth.
‡ All costs adjusted to year 2015 dollars and rounded to the nearest $100. Length of hospital stay data and actual cost data available for >99% of patients.
§ Totals are calculated separately for patients with type A and type B illness and then summed for the cumulative total; hence, Total (yrs) is not the product of the N \times Mean Stay Avoided (wks).

What is the IBTPP?

A program of the CA Department of Public Health that:

• Produces, maintains, stores and distributes BabyBIG® to all U.S. infant botulism cases and occasionally internationally (avail. 24/7/365 www.infantbotulism.org)

• Provides infant botulism consultation services to all physicians, hospitals, state and local health jurisdictions, laboratories and parents nationwide

• Investigates all cases of suspected infant botulism and related illnesses in CA with both laboratory and epidemiological methodologies
Questions?