**Infant Botulism: New Vistas 2018**

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**Disclosures**

Dr. Arnon has no relevant financial interests or commercial relationships to disclose.

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**Objectives**

At the end of this presentation attendees should be able to:

- Describe the typical features of infant botulism (IB)
- Understand basic laboratory aspects of IB diagnostic testing in California
- Be familiar with the standard-of-care treatment for IB, its method of action and its efficacy

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**Outline**

- What is the IBTPP?
- Overview of infant botulism
- Laboratory aspects of infant botulism diagnostic testing in California
- What is BabyBIG, its method of action and its efficacy?
- New vistas in infant botulism and botulinum toxin

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**What is the IBTPP?**

- A program within CDPH established by statute in 1995 (H&SC §123700 et seq.) that requires CDPH to:
  - Produce, maintain, store and distribute BabyBIG® to all U.S. infant botulism cases and occasionally internationally
  - Provide diagnostic laboratory services to all physicians, hospitals, laboratories and parents statewide
  - Investigate all cases of suspected infant botulism and related illnesses (these include some sudden infant death) with both laboratory and epidemiological techniques
  - Collaborate in scientific activities with other institutions intended to improve the study, prevention and treatment of infant botulism

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**Infant Botulism: What is it?**

- Temporary intestinal colonization by *Clostridium botulinum* (and rarely, neurotoxigenic *C. baratii* or *C. butyricum*) with production of botulinum toxin (BoNT) in lumen of colon
- Absorbed BoNT then causes flaccid paralysis and generalized muscle weakness with airway and swallowing difficulties
- Life-threatening: almost all patients require hospitalization for feeding and breathing supportive care. Approximately ½ the patients need ventilator care in pediatric ICUs.
- Affects infants less than 1 year of age
- Recognized only in 1976 and since 1980 the most common form of human botulism in the U.S.
Infant Botulism in the United States, 1976-2017

Exposures

- Honey is a natural reservoir of botulinum spores. However, over last decade, less than 5% of confirmed infant botulism cases had a prior honey exposure.
- Infant botulism is the reason that retail honeys are labeled, “do not feed to infants.”
- Most infant botulism patients likely acquire illness by swallowing spores carried by microscopic dust from the natural environment.

Laboratory testing

- Stool (or enema) specimen submitted to the Infant Botulism Laboratory at CDPH
- Mouse bioassay for BoNT
  - Gold-standard test
- Culture for neurotoxigenic Clostridia species

Laboratory testing FAQs

- Is dx testing necessary? – Yes
- Does treatment with BIG-IV prior to specimen collection affect testing? – No
- What specimen is required? – Fecal
- How much is needed, my patient is constipated? – As much as you can, but don’t delay submission
- How long until I receive results? – Morning following specimen receipt or as soon as positive results are available, whichever is sooner
- What is the cost to hospital? – No fee; this is a service provided by the State of CA

Please…

- Write on the lab orders and request your lab to expedite specimen shipment to IBTPP; fillable requisition form available on our website
- Do not wait for your patient to pass stool; administer an enema if necessary
- Stool needs to be collected in a sterile container, not a fixative or preservative vial; sterile urine collection container is best
What is BabyBIG?

• It’s Human Botulinum Immune Globulin, i.e., botulinum antitoxin/intact IgG
• BabyBIG (BIG-IV) a public service (i.e., not-for-profit) orphan drug available through consultation with IBTPP
• 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*

What is BabyBIG, cont.

• Botulism Immune Globulin Intravenous (Human) (BIG-IV; BabyBIG®) – approved 23 Oct 2003
• Made from plasma from volunteer donors boosted with botulinum immunogen (rBV A/B) to raise their anti-botulinum-toxin antibody levels
• Is the only approved treatment for patients with infant botulism type A and type B
• A new lot is made about every 5 years
• Only 1 lot is in distribution at any time

Efficacy of BIG-IV


Table 1. Hospital Stay and Costs Achieved with BIG-IV (BabyBIG®) Treatment of U.S. Infant Botulism Patients During its Pivotal Phase 3 Trial and, in 12 years Post-Licensure

<table>
<thead>
<tr>
<th>Treatment (wks)</th>
<th>Placebo group for phase 3 trial (C A)</th>
<th>Infant botulism patients treated with BIG-IV during the phase 3 trial (C A)</th>
<th>Infant botulism patients treated with BIG-IV in the first 12 years post-licensure (U.S.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Stay</td>
<td>63.0</td>
<td>59.0</td>
<td>1133.0</td>
</tr>
<tr>
<td>Total Stay</td>
<td>5.7</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Mean Cost‡</td>
<td>$207,500</td>
<td>$95,200</td>
<td>$118,600</td>
</tr>
<tr>
<td>Total Cost‡</td>
<td>–</td>
<td>$112,300</td>
<td>$88,900</td>
</tr>
<tr>
<td>Hospital Stay Avoided with BIG-IV Use</td>
<td>–</td>
<td>59.0</td>
<td>1133.0</td>
</tr>
<tr>
<td>Hospital Costs Avoided with BIG-IV Use‡</td>
<td>–</td>
<td>$95,200</td>
<td>$112,300</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 x Mean Stay Avoided (wks).
Benefits of BabyBIG

The mild case
1 month after infusion of BabyBIG

The severe case
11.5 months after infusion of BabyBIG

2018 Update on Novel Botulinum Toxin Serotypes /X and /En (with historical background)

Botulinum neurotoxin (BoNT)

BoNT mechanism of action

Origins of the BoNT toxin types (aka “serotypes”)

- 1910 Leuchs (Berlin)
  - Antisera raised vs. Clostridium botulinum Ellezelles strain culture filtrate (CF) toxin did not neutralize C. botulinum Darmstadt strain CF and visa-versa. Antitoxins made in horses.


Zeitschrift für Hygiene und Infektionskrankheiten 1910;65(1):55-84
Origins of the BoNT toxin type, cont.

- 1919 Burke (Stanford University)
  - Confirmed Leuchs’ finding using U.S. strains of *C. botulinum*
  - Named the two groups of strains and BoNTs “Type A” and “Type B”
  - Produced antitoxins in goats, rabbits
  - Defined antitoxin potency in terms of guinea pig minimum lethal doses (MLDs) neutralized
  - 8 serotypes A-H known as of 2013

3-domain functional structure of BoNT

Turning now to novel BoNT/X and novel BoNT/En

Botulinum Neurotoxin /En (found in bovine *Enterococcus faecium*)

Are BoNT/X and BoNT/En novel botulinum toxins?

**Points for**
- Has DNA sequence very different than BoNTs/A-H
- Has the 3-domain LC, HN, HC structure of the BoNTs
- Cleaves VAMP substrate, as does BoNTs/B, D, F, G
- Cleaves VAMP at a residue pair different from all other BoNTs
- Very large amounts will enter cultured neurons
- Very large amounts will produce local paralysis in mice (~10^6 x required vs. BoNTs/A-H)

**Points against**
- Has DNA sequence very different from BoNTs/A-H
- Work reported in August 2017 and February 2018 done with LC and HN-HC fragments expressed in E. coli
- boNT/x and boNT/En sequences appears to lack HCC binding structure needed for mammalian neurons
- Culture filtrates from C. botulinum source strain minus NT/B plasmid does not make mice sick
- Are BoNT/X and BoNT/En expressed by its C. botulinum and E. faecium source strains?

**Perspectives**
- The recently reported BoNT/X and BoNT/En gene sequences, when expressed in E. coli, display capabilities consistent with known BoNTs
- However, culture filtrate (CF) of the source C. botulinum strain 111 do not produce botulism illness in mice
- Toxigenicity of CF of E. faecium BoNT/En is unknown
- Hence, the jury is still out as to whether BoNT/X and BoNT/En should be considered true illness-producing BoNTs or should just be termed "botulinum-like" proteins

**Thank you and Questions?**