Two Cases of Infantile Botulism in Virginia that Highlight the Importance of Early Clinical Diagnosis and Proper Reporting, Treatment, and Prevention.

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Purpose:

Infantile botulism is a rare condition that primarily affects infants under the age of 6 months. This disease is caused by ingestion of Clostridium Botulinum spores that are found in soil or honey. Once ingested, the spores germinate into bacteria that colonize the infant's immature intestinal tract and synthesize a toxin. This toxin irreversibly binds acetylcholine receptors, leading to the clinical presentation of progressively worsening constipation, weakness, hypotonia, poor feeding, weak cry, and decreased activity. If enough toxins are released, life-threatening flaccid paralysis with respiratory failure can ensue. Fortunately, with high clinical suspicion, a physician can gain access to life-saving Botulism Immune Globulin Intravenously (BIG-IV) prior to laboratory confirmation. Early administration of Botulism Immune Globulin Intravenous (BIG-IV) can significantly improve outcomes by neutralizing any systemically circulating botulinum toxin. With early diagnosis and treatment, full recovery without neurologic sequelae is likely. Here we present two infants from Southwest Virginia who were admitted to a children's hospital. These cases illustrate the typical presentation of infantile botulism, an approach to management, the possible clinical course, and opportunities for prevention.

Case Summaries

Case 1

A previously healthy 5-week-old Caucasian male was taken to his primary care provider (PCP) for poor feeding and decreased activity. His mother reported that he was in his normal state of health until 2 days prior when he was noted to be increasingly somnolent. He was too weak to suck and had started to refuse the bottle. She also described a weak cry. These symptoms continued to progress until she noticed increased work of breathing. Review of systems was positive for decreased urination and stooling with his last bowel movement being two days

ago. She denied any fever, congestion, cough, vomiting or seizures. He was breast fed with formula supplementation and had not been introduced to any other foods or had any other ingestions. She denied sick contacts. His past medical history was notable for a 2-week NICU stay for jaundice, hypoglycemia and respiratory distress after being delivered via C-section at 37 weeks. He received his Hepatitis B vaccination prior to discharge without complication.
On physical exam at his PCP's office, his vitals were normal. He was noted to be somnolent and mottled with poor tone, a weak gag, and minimal suck. These findings prompted immediate transport to a tertiary medical center.

In the Emergency Department (ED), he was still afebrile with normal vital signs. His physical exam revealed hypotonia with poor head control. He had a weak cry and inadequate swallow. A broad work-up was pursued in line with the differential diagnosis. A septic work-up, including lumbar puncture returned reassuring results. The patient had no electrolyte abnormality, a negative urine drug screen, a normal brain CT, and an unremarkable X-ray of the chest and abdomen. He received intravenous fluids and antibiotics and was transferred to the pediatric intensive care unit (PICU) for further evaluation and treatment.

In the PICU, results continued to come back normal, including ammonia, thyroid stimulating hormone (TSH), lactate, and homocysteine. His newborn screen was tracked down and was normal. The Infant Botulism Treatment and Prevention Program in California (IBT&PC) (2020a) was called shortly after admission and recommended further work-up and a neurology consult, feeling that a longer history of constipation would be likely if this was botulism. His EEG was normal, EMG was unavailable for infants his age at this institution and the neurologist suspected botulism. The approval process for treatment with BIG-IV was started after consultation with the Virginia Department of Health, Centers for Disease Control (CDC), and stakeholders at the IBT&PC. A sterile enema was used to obtain a stool sample for botulinum toxin testing following a strict protocol on sample collection. On day 2 of hospitalization, the patient's respiratory distress worsened, and he was placed on BIPAP which progressed to intubation by day 3. Meanwhile, approval was granted for treatment with BIG-IV and it was sent to the patient's medical center and administered that evening.

The patient tolerated BIG-IV administration without complication. On day 4 of admission, he had zero respiratory drive, no motor response to stimulation, minimal eye-opening and no cough or gag reflex. On day 5, he showed mild improvement in symptoms, but developed a fever and was treated for ventilator-associated pneumonia. Three days post-BIG IV treatment, the patient regained his gag, suck, and cough reflexes and had improved tone, moving all of his extremities. He also began having multiple bowel movements a day with the help of polyethylene glycol and glycerin suppositories. The patient was extubated on hospital day 7, returned a positive *Clostridium botulinum* test on day 10, and discharged home on hospital day 21 with nasogastric gavage feedings. Neurologically, he has made a full recovery.

During his hospital stay, additional history uncovered that the mother's fiancé worked for a concrete company and regularly came home covered in concrete, mud, and dirt. He rarely changed clothes or removed his shoes prior to entering the home. We believed this to be the source of our patient's exposure.

Case 2

A previously healthy 4-week-old Latino male was taken to his PCP multiple times over a week for constipation. Several home interventions such as rectal stimulation and Karo syrup added to his formula were unsuccessful. During the second week of his constipation, he started to have signs of poor feeding and was taken to the emergency department (ED) where the mother reported decreased oral intake and urine output. She also reported a weak cry and less activity. In the ED, he received an abdominal x-ray that was normal and IV fluids for dehydration. The family was discharged home with return precautions. He returned to the ED less than 4 hours after discharge with continued concerns. He had had one small dark bowel movement after a suppository. He was not taking any formula and his activity levels had continued to decline. He was no longer interacting with his caregivers, and they noticed that he was weaker. Review of systems was otherwise negative for cough, congestion, vomiting or fever. Past medical history revealed a previously healthy male born at 37.6 weeks via caesarean section without complications. He had received Hepatitis B immunization without adverse reaction and had a normal newborn screen. The mother denied any sick contacts or ingestions other than formula.

He lived with his mom, dad, and older siblings and also spent time at his grandparents' house where there was ongoing construction inside and outside the home.

On physical exam, the ED physician noted a sunken fontanelle, dry mucous membranes, a weak cry, sluggish capillary refill, decreased eye tracking, and global hypotonia. He was found to be hypothermic and tachycardic on vital signs but was not in respiratory distress. Given his presentation, he was given IV fluids and empiric antibiotics following blood, urine and spinal fluid cultures. Because of his lethargy, the PICU was consulted for admission. He did not have increased white blood cells in his blood, urine or spinal fluid. He also did not have an electrolyte abnormality or elevated lactate or ammonia to suggest an inborn error of metabolism. There was no history of trauma and a head CT was unremarkable. He had a nasogastric (NG) tube placed to provide enteral nutrition and was admitted to the PICU.

Prior to admission to the PICU, the clinical suspicion for botulism was high. The Infant Botulism Prevention and Treatment Center (2020a) was contacted. They agreed this patient had a high suspicion for infantile botulism and sent BIG-IV the next morning. He had no clinical signs of improvement until day 4 of hospitalization when he showed improved strength and mental status. By day 5, he was tolerating all his feeds orally and his nasogastric tube was removed. On day 7, he was discharged home with near baseline status and no further interventions at home. Five days after being discharged home, his stool became positive for *Clostridium botulinum* toxin B.

Discussion:

Infantile botulism is caused by neurotoxins released into an infant's circulation following the ingestion of *Clostridium botulinum* spores. The Clostridium bacteria is an obligate anaerobe that is a spore-forming gram-positive bacillus. It produces a heat-labile neurotoxin that is the most potent toxin known on planet earth. Clostridium can produce 7 different toxins, identified as A-G with some debate about an 8th (H). The vast majority of infantile botulism cases are from neurotoxin A and B. Infantile botulism is more common than both food and wound botulism combined (Cox & Hinkle, 2002; American Academy of Pediatrics, 2018).

The botulinum toxin disrupts the release of acetylcholine from the presynaptic neurons and prevents muscle excitation and contraction (American Academy of Pediatrics, 2018). When 70% of terminals are impaired, the disease begins to manifest itself. Common symptoms are constipation, weakness, hypotonia, cranial nerve impairment, including ptosis, sluggish pupillary reflex, weak gag, cry, suck and difficulty swallowing. These can be vague complaints and ones often heard in the pediatric office. It is not until 90% of the neuromuscular terminals are impaired that you will start to have respiratory failure and flaccid paralysis. Around half of all infants with infantile botulism will require mechanical ventilation (Clemmens & Bell, 2007). The presentation is predictable once a certain level of toxemia is reached. It is always a descending, bilateral, symmetric, flaccid paralysis.

Due to the vague nature of these presenting symptoms and the low incidence, infantile botulism is often misdiagnosed in the early stages of the disease (Francisco & Arnon, 2007) Patients are often seen multiple times and undergo extensive workups as lethargy progresses (Infant Botulism Treatment & Prevention Program, 2020a). *Clostridium botulinum* infection should be on the differential diagnosis of an infant presenting with subacute progression of motor weakness, lethargy, poor feeding, and constipation. Workup should evaluate for infection, inborn errors of metabolism, non-accidental trauma, spinal muscular atrophy, electrolyte derangements, hypothyroidism, and other toxic ingestions. By excluding these other possibilities and narrowing your differential, you will be able to solidify your suspicion of infantile botulism and proceed with appropriate management.

Summary Recommendation:

Management and Treatment:

Botulism is at first a clinical diagnosis. Management of infant botulism consists of both supportive care and the administration of the botulism antitoxin, Botulism Immune Globulin Intravenous (BIG-IV)**.** You should not wait for laboratory confirmation to begin treatment. BIG-IV neutralizes all circulating toxins, stopping the progression of the disease while the body regenerates motor neurons (Infant Botulism Treatment & Prevention Program, 2020b; Thompson, Filloux, & Van Orman, 2005). To obtain the antitoxin expeditiously, you should

contact both your state health department and the Infantile Botulism Treatment and Prevention Center in California (Figure 1) (Infant Botulism Treatment & Prevention Program, 2020b; Centers for Disease Control, 2020). The state health department will assist in obtaining the stool specimen using a strict collection protocol (Virginia Department of Health, 2019). They will also help coordinate with the IBT&PC, which is the gatekeeper for the national supply of the antitoxin.

The infant should fully recover from the illness with appropriate supportive care with or without treatment with BIG-IV. In a 5-year randomized, double-blinded, placebo-controlled trial, however, there was a substantial decrease in all measures of disease-associated morbidity with the use of immune globulin in the first few days of admission. The length of intensive care stay, mechanical ventilation, and tube feedings were decreased and the most significant of these reductions was the length of the average hospital stay from 5.7 weeks to 2.6 weeks in the treatment group ($P<0.001$) (Arnon, 2007; Long, 2007; Arnon et al., 2006). To date, there have not been any reported studies showing significant adverse effects associated with BIG-IV. This risk to benefit ratio strongly supports early administration of the drug **(**Arnon et al., 2006).

Most cases are treated in the intensive care unit as around 50% of cases will need respiratory support. Since it also affects the cranial nerves, successful swallowing can become compromised and affected patients are at risk of aspiration and metabolic derangements (Cox & Hinkle, 2002; Clemmens & Bell, 2007; Long, 2007). Supportive care should be given via intravenous fluids and nasogastric tube feedings when appropriate. The prognosis is excellent with appropriate supportive care **(**Arnon et al., 2006). Recovery is progressive as it takes time to replenish the motor endplates **(**Infant Botulism Treatment & Prevention Program, 2020a). Diaphragmatic function tends to recover before peripheral muscles allowing the patient to come off respiratory support and transfer out of the ICU as they make their full recovery (Cox & Hinkle, 2002).

Public Health Message and Prevention:

Most cases of infant botulism have no definitive source of exposure and can be very difficult to fully prevent because the bacteria is found naturally in the soil and dust. There are, however, measures that can be done to reduce the likelihood of exposure. The most common preventive

measure is not to expose an infant to honey or honey products prior to the age of one. This is an absolute recommendation. Honey can contain the bacteria even after processing. Honey is safe only for people over the age of one as the botulism spores are no longer dangerous to a healthy and mature digestive tract. A detailed history should include asking about honey consumption. Per the Redbook on Pediatric Infectious Diseases, the incubation period can be between 3-30 days (American Academy of Pediatrics, 2018).

Unfortunately, more than 85% of infants have no honey exposure and other causes should be investigated. Since Clostridium spores are naturally occurring in the soil, it is important to ask about the occupation of all caregivers and any recent construction in or near the home. Occupations such as construction workers, excavators, farmers, and those employed in concrete and masonry are at high-risk of bringing spores into the home. Both of our cases had no exposure to honey but had a parent or caregiver in a high-risk occupation.

Most cases of infantile botulism worldwide are diagnosed in the United States with greater than 50% of cases being in California (Centers for Disease Control & Prevention, 2016). Clostridium botulinum spores have been found in the soil in all 50 states. Cases in Virginia have been primarily caused by toxin B with some reports of toxin A (Centers for Disease Control & Prevention, 2016). The cases in Virginia historically have all been responsive to the BIG-IV.

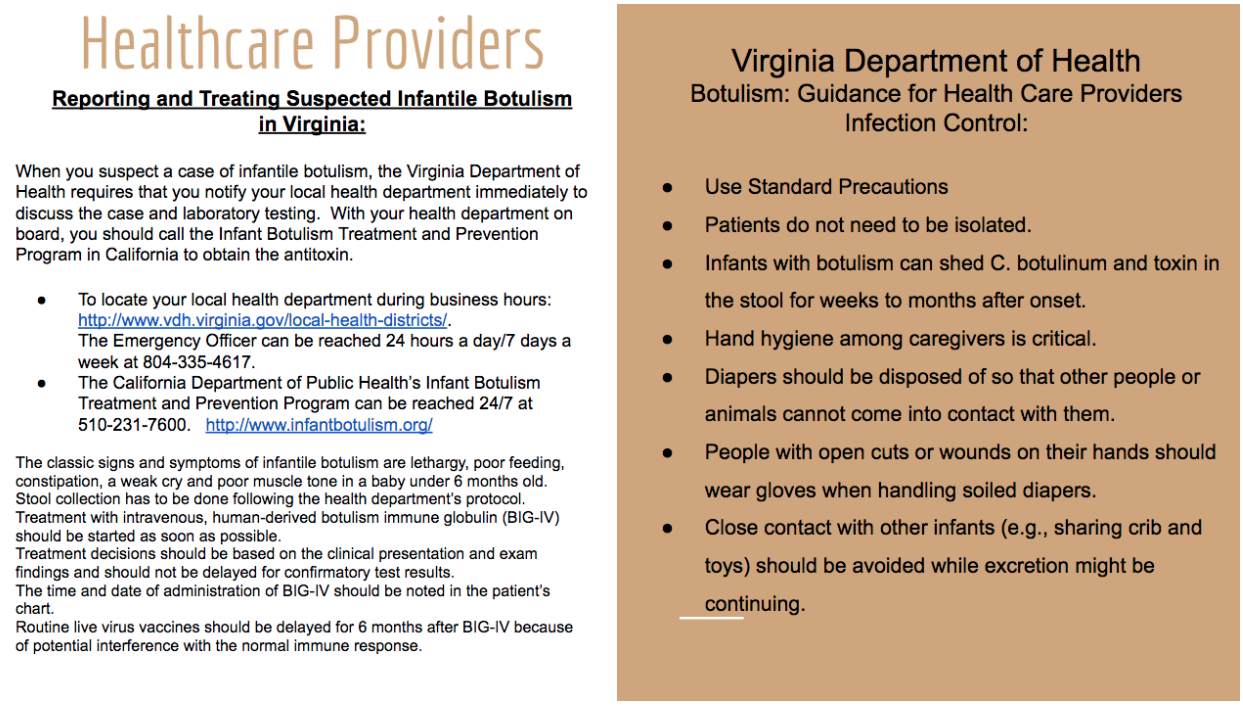
It is important for health care providers to ask about caregiver occupations and childcare arrangements at each visit. If a parent or caretaker is employed in a high-risk occupation, health care providers should take time to educate families on the risk factors for exposure to infants. They should be advised to remove work boots outside and remove all work clothes prior to contact with the infant. A clean breast milk or formula prep area is important and those preparing the bottle should be aware of possible exposures. If there is any construction near or in the home, homeowners should make sure all windows are shut and the area where the infant's food is prepared should be protected from any dust or dirt contamination (Figure 2).

While still rare, infantile botulism exists in Virginia. It is the responsibility of the medical and public health teams to identify high-risk families, educate them on prevention strategies, identify

botulism cases and initiate timely, appropriate treatment. A good social and occupational history is important as honey consumption is not the most common way to contract the disease. Nailing the diagnosis of infantile botulism and initiating timely treatment will expedite a full, sweet recovery.

Figure 1:

Reporting Suspected Infantile Botulism and Obtaining BIG-IV in Virginia:



Healthcare Providers

Reporting and Treating Suspected Infantile Botulism in Virginia:

When you suspect a case of infantile botulism, the Virginia Department of Health requires that you notify your local health department immediately to discuss the case and laboratory testing. With your health department on board, you should call the Infant Botulism Treatment and Prevention Program in California to obtain the antitoxin.

- To locate your local health department during business hours: http://www.vdh.virginia.gov/local-health-districts/.
  The Emergency Officer can be reached 24 hours a day/7 days a week at 804-335-4617.
- The California Department of Public Health's Infant Botulism Treatment and Prevention Program can be reached 24/7 at 510-231-7600. http://www.infantbotulism.org/

The classic signs and symptoms of infantile botulism are lethargy, poor feeding, constipation, a weak cry and poor muscle tone in a baby under 6 months old.
Stool collection has to be done following the health department's protocol.
Treatment with intravenous, human-derived botulism immune globulin (BIG-IV) should be started as soon as possible.
Treatment decisions should be based on the clinical presentation and exam findings and should not be delayed for confirmatory test results.
The time and date of administration of BIG-IV should be noted in the patient's chart.
Routine live virus vaccines should be delayed for 6 months after BIG-IV because of potential interference with the normal immune response.

Virginia Department of Health

Botulism: Guidance for Health Care Providers

Infection Control:

- Use Standard Precautions
- Patients do not need to be isolated.
- Infants with botulism can shed C. botulinum and toxin in the stool for weeks to months after onset.
- Hand hygiene among caregivers is critical.
- Diapers should be disposed of so that other people or animals cannot come into contact with them.
- People with open cuts or wounds on their hands should wear gloves when handling soiled diapers.
- Close contact with other infants (e.g., sharing crib and toys) should be avoided while excretion might be continuing.

Figure 2:

Caregiver Handout on Preventing Infantile Botulism:

References:

American Academy of Pediatrics (2020). *Botulism and infant botulism*. Retrieved from https://redbook.solutions.aap.org/chapter.aspx?sectionid=189640068&bookid=2205

Arnon, S.S. (2007). Creation and development of the public service orphan drug-human botulism immune globulin. *Pediatrics, 119*(4), 785-789.

Arnon, S.S., Schechter, R., Maslanka, S.E., Jewell, N.E., & Hatheway, C.L. (2006). Human botulism immune globulin for the treatment of infant botulism. *New England Journal of Medicine, 354*: 462-471

Centers for Disease Control and Prevention (CDC). (2017). *National botulism surveillance summary 2016.* Retrieved from https://www.cdc.gov/botulism/pdf/Botulism-2016-SUMMARY-508.pdf

Centers for Disease Control and Prevention (CDC). (2020). National notifiable diseases surveillance system case definitions. Retrieved from https://wwwn.cdc.gov/nndss/conditions/botulism/

Cox, N. & R. Hinkle, R. (2002). Infant botulism. *American Family Physician, 65*(7), 1388-1392.

Francisco, A.M.O. & Arnon, S.S. (2007). Clinical mimics of infant botulism. *Pediatrics, 119*(4) 826-828

Infant Botulism Treatment and Prevention Program. (2020a). *Clinical diagnosis*. Retrieved from http://www.infantbotulism.org/physician/clinical.php

Infant Botulism Treatment and Prevention Program: Patient management. (2020b). Retrieved from http://www.infantbotulism.org/physician/patient.php

Long, S.S. (2007). Infant botulism and treatment with BIG-IV (BabyBIG). *The Pediatric Infectious Disease Journal, 26*(3), 261-262.

M.R. Clemmens, M.R. & Bell, L. (2007). Infant botulism presenting with poor feeding and lethargy. *Pediatric Emergency Care, 23*(7), 492-494.

Thompson, J.A., Filloux, F.M., & Van Orman, C.B. (2005). Infant botulism in the age of botulism immune globulin. *Neurology, 64*(12), 2029-2032

Virginia Department of Health (VDH). (2019). Botulism: Guidance for healthcare providers. Retrieved from http://www.vdh.virginia.gov/content/uploads/sites/3/2019/02/Botulism_ClinGuid_2019.pdf

**For more information about infant botulism, BabyBIG® (BIG-IV) and the Infant Botulism and Treatment Program, please visit the websites listed below:*

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/InfantBotulism.aspx

http://www.infantbotulism.org/