Infant Botulism: A Review of Two Cases Reported in 2008 from El Paso, Texas

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ABSTRACT
Botulism is a rare and very serious neuroparalytic illness caused by a potent toxin produced by the organism Clostridium botulinum. Of the four forms of botulism (foodborne, wound, infant, and adult intestinal toxemia), infant botulism is the most common. Infant botulism is a complex syndrome that can be manifested by a broad spectrum of symptoms that can sometimes be mistaken for benign illnesses. If not recognized early, the illness is associated with high morbidity. This article will present two hospitalized cases of infant botulism that were reported in year 2008 in El Paso, Texas. Both cases were laboratory confirmed with type A botulism. One of the two infants received human botulism immunoglobulin.

INTRODUCTION
Infant botulism is an uncommon disease that occurs when ingested spores of Clostridium botulinum germinate, colonize, and produce botulinum neurotoxin in the lumen of the large intestine. Since 2001, approximately 80 to 145 cases of infant botulism have been reported annually in the United States.

Infant botulism occurs predominately in infants younger than 6 months of age; however, there have been reports of cases being a few days old through 12 months of age. The initial presentation of infant botulism begins with constipation, and manifests as poor feeding, weak suck, decreased spontaneous movement, loss of facial expression, weak cry, diminished gag reflex, ptosis, poor head control, difficulty swallowing, abnormal eye movements, dilated and/or sluggishly reactive pupils, and progress to generalized flaccidity and respiratory compromise. The severity of the illness may vary from mild lethargy and slowed feeding to sudden infant death.

This article will present two cases of infant botulism that were reported in year 2008 in El Paso, Texas. Both cases were laboratory confirmed with type A botulism. One of the two infants received human botulism immunoglobulin.

El Paso is located in the United States, at the western tip of Texas, where it, New Mexico, and Mexico come converge. About 734,669 people live in El Paso County, which makes it the 6th largest county in Texas and 74th in the Unites States. The city of El Paso has a population of 606,913 and is the 6th largest city in Texas and 21st most populous in the nation. About 81% of El Paso’s population is of Hispanic origin. From 2001 to 2005, El Paso County averaged 14,280 live births per year. The city’s elevation is 3,800 feet above sea level, and is surrounded by the Chihuahuan Desert.

CASE REPORTS
Patient 1

A 3-month-old female with no history of serious medical problems was well until 2 days prior to hospital admission, when she presented with upper respiratory infection symptoms, decreased appetite, and lethargy. The infant was seen by her pediatrician, and directly admitted to the hospital with a diagnosis of bronchiolitis and dehydration.

On admission, the infant was noted to be very lethargic and was transferred to PICU for further workup and treatment. The infant was noted to have decreased urine output, poor suck and swallow, weak cry, and continued to be lethargic despite fluid resuscitation. On day 2 of admission, the infant began to have fever and decreased reactivity. During a lumbar puncture, the infant went into respiratory distress and was intubated and started on vancomycin and cefotaxime. A nasogastric tube was also placed. Cerebral spinal fluid (CSF), blood, and urine cultures were negative. A nasal washing did come back positive for respiratory syncytial virus (RSV). On day 3 of admission, the infant was anemic and transfused with packed red blood cells. On day 4 of admission, a serum and stool culture for Clostridium botulinum was requested. An MRI brain scan without contrast and a brain CT scan was performed and read as negative. On day 5, an electromyography was performed and showed mild decreased conduction velocities suspicious for infantile myasthenia gravis but not consistent with botulism. There were no decrements or increments seen on repetitive stimulation. The infant was still presenting as hypotonic, lethargic, with slow deep tendon reflex, and ptosis. On day 6 of admission, the infant was medicated with BabyBig® and vancomycin discontinued. On day 7 of admission, the infant was again anemic and was transfused with packed red blood cells. The infant had not stools for 5 days. The decision was made to transfer the infant to a tertiary care center with neurology consultation for further workup and treatment for probable infant botulism and rule-out infantile neuromuscular disease.

At the tertiary care center, an attempt was made on day 10 to extubate the infant, but re-intubation was necessary 24 hours later due to hypotonia and thick respiratory secretions. A second attempt was made on day 19, and the infant was extubated to synchronized inspiratory positive airway pressure (SIPAP) and slowly weaned to room air on day 22. The infant continued to be RSV positive, which may have contributed to her respiratory morbidity. Direct fluorescent-antigen detection for RSV was negative on day 17. The infant was discharged with physical, speech, and occupational therapy follow-up. Twenty-eight days after stool, collection the test results came back positive for C. botulinum toxin type A. Overall, the infant required a total of 24 days of PICU care, 18 days of intubation with respiratory support, 27 days of nasogastric tube feeding, and 31 days of hospitalization.

Prior to hospitalization, the infant was breast-fed during the nights and fed formula during the day. She had no history of honey ingestion. The family lived in an apartment. No construction around apartment complex was noted by family. The mother received no prenatal care during her pregnancy. The infant was a product of normal gestation and delivery. The infant fell ill in late January.

Patient 2

A 5 ½-month-old male with no history of serious medical problems was well until 3 days prior to hospital admission when he suddenly presented with neck retraction to one side. He was seen by his pediatrician who advised his parents to come back if the symptoms continued. He was seen once again by the pediatrician and referred to the hospital for sepsis, intussusception, and meningitis evaluation. On admission, the infant presented with a weak suck, weak cry, fussiness, and neck retraction to one side. The infant was admitted to the pediatric floor where therapy for possible sepsis or meningitis was initiated (vancomycin and cefotaxime). On day 2 of admission, the infant was transferred to pediatric intensive care unit (PICU) with
lethargy, poor stimulus response, nonreactive pupils, complete head lag, weak cry, drooling, poor gag reflex, and generalized flaccidity. All cultures (cerebral spinal fluid [CSF], blood, and urine) were negative. Serum arbovirus and lyme testing were negative, CSF enterovirus testing was negative, urine drug toxicology was negative, and no lead levels in blood were detected.

On the 3rd day of admission, the infant was given a clinical diagnosis of Guillain-Barre syndrome versus tick paralysis versus botulism versus meningitis or encephalitis. A stool culture for Clostridium botulinum was requested. Brain computed tomography (CT) scan, magnetic resonance imaging (MRI) brain scan, head ultrasound, and an abdominal sonogram were all normal. The infant progressively worsened, and on the 5th hospital day, was intubated and placed on a ventilator due to transient apnea. Ventilator support was continued for 7 days and weaned to nasal cannula. A nasogastric tube (NGT) was also placed into infant for 16 days due to weak suck and gag. The infant had also not stools for 3 days.

The infant did not receive Human Botulism Immune Globulin (BabyBIG®) because of a delay in diagnosis and contacting the Local or State Public Health Department. The infant remained in PICU for a total of 13 days, and was transferred to the pediatric floor for continuity of care, speech therapy, and occupational therapy. The infant was discharged on the 21st day of hospitalization with speech and occupational therapy follow-up. Eighteen days after stool collection, the test results came back positive for 

The infant had no travel history and fell ill in early April.

**DISCUSSION**

Botulism is a rare and very serious neuro-paralytic illness caused by a potent toxin produced by the organism *Clostridium botulinum*. Of the four forms of botulism (foodborne, wound, infant, and adult intestinal toxemia), infant botulism is the most common.21 The most recent report by the Council of State and Territorial Epidemiologist Botulism Surveillance noted that 106 cases of infant botulism had been reported by 23 states in year 2006.8

The incubation period for infant botulism is not truly known, but is believed to be between 3 to 30 days. Coincidently both cases reported in year 2008 were born on the same date and hospital. The infants were born in late October of 2007. The ingestion of honey has been associated with infant botulism cases.22,23 Honey should not be offered to infants under 12 months of age. For the majority of the cases, the source of ingestion is unknown approximately 85% of the time.24 Neither of the infants had a history of consuming honey. Both were partially breast-fed and lived in apartments. One of the parents worked as a construction worker, but had not been employed for 1 month.

Infant botulism can be manifested by a broad spectrum of symptoms that early in the disease may mimic those of sepsis, dehydration, viral syndrome, pneumonia, idiopathic hypotonia, meningitis, failure to thrive, hypothyroidism, metabolic encephalopathy, amino acid metabolic disorder, heavy metal poisoning (Pb, Mg, As), electrolyte imbalance, drug ingestion, poliomyelitis, medium-chain acyl-CoA dehydrogenase, brain stem encephalitis, myasthenia gravis, viral polyneuritis, Guillain-Barré syndrome, Hirschsprung disease, or Werdnig-Hoffman disease. Sepsis is the most common initial diagnostic consideration9,23,25-27

In 1989 the California Department of Health Services (CDHS) developed an orphan drug Human Botulism Immune
Globulin Intravenous (BIG-IV) for the treatment of infant botulism caused by toxin type A or B. The immunoglobulin is derived from pooled adult plasma from persons immunized with pentavalent botulinum toxoid. In a 5-year placebo-controlled, double-blinded randomized clinical trial BIG-IV treatment reduced the length of hospital stay by 31 weeks, duration of intensive care by 32 weeks, duration of mechanical ventilation by 26 weeks, duration of tube or intravenous feeding by 64 weeks, and hospital charges per patient by $88,000 U.S. dollars (in year 2004).28 In 2003, after a subsequent 5-year nationwide open-label study, BIG-IV was licensed by the US FDA for sale by the CDHS as BabyBig® (24-hour a day, 7 days a week telephone: 510-231-7600). The treatment is administered as a single intravenous infusion, and is only available for use in those who are diagnosed within 7 days of hospital admission. Treatment given within 3 days of hospital admission is more effective than that at 4 to 7 days of hospitalization.28 BabyBig® at $45,300 (February 2008 cost) can be cost-effective if given promptly.

The two cases had admitting diagnosis of bronchiolitis/dehydration and sepsis. Infant botulism was suspected on day three and four of hospital admission. Unfortunately, this time span can be too long. The detection of infant botulism must be almost immediate if treatment is to be effective. Before BabyBig® is released by DSHS, a purchase agreement must be signed by the institution receiving the immunoglobulin. Shipment must also be taken into consideration if not in proximity to DSHS. If everything goes well, obtaining treatment may take about 24 hours.

BabyBig® has a half-life of approximately 28 days; thus, a single infusion will immediately provide a protective level of neutralizing antibodies and continue circulating for 6 months.28 This particular feature can be of importance when considering treatment of secondary bacterial infections. It is believed that antibiotics may worsen infant botulism by the abrupt lysis of C. botulinium vegetative cells in the intestinal lumen, causing a massive release of neurotoxin available for absorption. In particular, aminoglycosides should be avoided, because they appear to play a role in potentiating the neuromuscular blocking effects of botulinum toxin.23,29 Patients receiving the immunoglobulin will neutralize any toxemia that might result from the use of a non-aminoglycoside antibiotic such as sulfamethoxazole-trimethoprim, which has been shown to be resistant to Clostridium botulinum.28,30

Of the two cases presented, one of them did not receive immunoglobulin due to the fact that the physicians were awaiting laboratory confirmation of C. botulinum. The mouse lethality assay is the standard test for the detection of botulinum toxin, and it can take a couple of days to obtain results. BabyBig® therapy is time sensitive, and should be administered promptly to diminish the morbidity and expense associated with this life-threatening disease. Treatment should be based on clinical diagnosis and not delayed for laboratory confirmation.

Physicians are reminded that botulism or suspected botulism (all forms) is an immediately reportable illness to local and state health authorities. Contact information for State Health Departments in the United States can be obtained from the following web site http://www.cdc.gov/mmwr/international/relres.html.

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REFERENCES