

MINIREVIEW

Association Between Honey Consumption and Infant Botulism

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Infant botulism, a disease that results in a blockade of voluntary motor and autonomic functions, was first recognized in the United States in the late 1970s. Since then, more than 1000 cases in this country have been reported to the Centers for Disease Control and Prevention (CDC). Numerous studies have shown that the ingestion of honey is linked with infant botulism. In addition, honey samples across the United States have tested positive for *Clostridium botulinum* spores and toxins. Such substantial evidence led the CDC to recommend that honey not be given to infants younger than 12 months old. It is important that clinicians be familiar with this risk and should not recommend honey-containing products or supplements or the use of honey as a flavoring agent for infants in this age group. (Pharmacotherapy 2002;22(11):1479–1483)

Honey should not be given to infants younger than 12 months old.^{1–4} This recommendation is supported by major pediatric and public health organizations, as well as manufacturers of honey in the United States. Natural products are consumed by approximately 14% of the U.S. population.⁵ However, many parents are unaware of the potential danger of honey and administer it to their infants. Honey may be a reservoir for *Clostridium botulinum* spores, which have been linked to the development of infant botulism. Clinicians should become familiar with the risks associated with honey and should not recommend honey-containing supplements or the use of honey as a flavoring agent for children less than 12 months old.

Clostridium botulinum is ubiquitous in the environment but is found primarily in soil and marine sediment.³ It is a gram-positive, anaerobic, spore-forming bacterium that produces seven distinct neurotoxins, labeled A through G. Toxins A, B, and rarely, E, are

responsible for causing disease in humans.^{1, 2} *Clostridium botulinum* spores and toxin are carried by dust particles and deposited on fresh fruits, vegetables, and other agricultural products, including honey. Ingestion of foods contaminated with these preformed toxins or spores may result in the development of human botulism.^{1, 2} *Clostridium botulinum* spores are dormant forms of the bacteria that can survive under harsh conditions, such as elevated temperatures (> 100°C), which enables them to thrive during food preservation procedures. In contrast to the spores, the toxin produced by *C. botulinum* is heat labile and easily destroyed by temperatures above 80°C.³ Acidic environments also inhibit the growth of *C. botulinum* and its spores.

Infant botulism occurs after ingestion of *C. botulinum* spores.^{1–3} These spores germinate within the child's large intestine, multiply rapidly, and release neurotoxins responsible for infant botulism, primarily A and B. Once absorbed, these neurotoxins bind to cholinergic synapses, resulting in a blockade of voluntary motor and autonomic junctions. Within 18–36 hours of ingestion of contaminated food, this blockade manifests symptomatically as a symmetric, descending, flaccid paralysis of motor and

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Table 1. Documented Cases of Honey Ingestion and Infant Botulism in the United States

Age of Onset	No. of Infants	No. of Associated Toxins	No. of Infants with History of Honey Consumption	Positive Honey Sample
5–20 wks ⁶	6	3 type A 3 type B	3	1 jar
Not reported ⁷	43	Not reported	13	3 jars
3–35 wks ⁸	81	47 type A 34 type B	29	None analyzed
Not reported ⁹	41	25 type A 16 type B	12	6 jars
2–50 wks ¹⁰	68	33 type A 35 type B	11	None analyzed

autonomic nerves.¹ Constipation is often the first symptom in infants with botulism and usually precedes the onset of neurologic symptoms by a few days. Over time, the infant appears lethargic, feeds poorly, and develops a weak cry and poor muscle tone. Symptoms progress to paralysis of the arms, legs, trunk, and respiratory muscles. If left untreated, infant botulism can be fatal.^{1–3}

Epidemiology

Infant botulism was first recognized in the United States in 1976. Since then, the frequency of the disease has been on the rise, with 1442 cases reported to the Centers for Disease Control and Prevention (CDC) from 1976–1996.⁴ The majority of these cases were from California (~50% of all cases), Delaware, Utah, and Hawaii. They involved primarily type A and B neurotoxins, which accounted for 46.5% and 51.9% of cases, respectively. Approximately 95% of infant botulism cases occur in infants less than 6 months old; the remaining 5% occur in infants 6–12 months old. The disease is distributed equally between boys and girls and across all major racial and ethnic groups. Risk factors for infant botulism are poorly understood; however, several studies have linked the ingestion of honey to the development of infant botulism (Table 1).^{6–10}

Honey Consumption and Infant Botulism in the United States

A prospective study was conducted in 1977 to identify any commonalities among the first six infants in the United States diagnosed with infant botulism.⁶ Age of onset, type of *C. botulinum* toxin responsible for disease, and food and drugs ingested before disease onset were evaluated.

The infants ranged in age from 5–20 weeks old. Type A botulinum toxin caused the disease in three infants and type B was responsible in the other three. Fifteen food and six drug items ingested by the infants were tested, including mother's breast milk, honey, rice cereal, oatmeal, infant formula, pediatric vitamin preparations, pediatric iron supplements, and acetaminophen drops. Of these items, only a jar of honey tested positive for *C. botulinum*. This food item had been fed to one infant as a honey-and-water mixture. Two of the remaining five infants also had been fed honey, but no *C. botulinum* was isolated from tested samples.

From 1976–1978, California reported 43 documented cases of infant botulism. In 13 of these cases, infants had ingested honey before disease onset; *C. botulinum* was isolated from three honey samples fed to the affected infants. The CDC also reported on the testing of honey specimens in California. Approximately 60 specimens were tested, with 13% testing positive for *C. botulinum*. In 1978, the CDC reported the association between honey consumption and infant botulism.⁷ They concluded that honey may have been the source of infection in approximately one third of the cases reported and therefore should be avoided as a food source for all infants younger than 12 months old.

A retrospective analysis of infant botulism cases reported to the CDC from January 1, 1975, to July 31, 1978, was performed to assess epidemiologic characteristics of the disease.⁸ A total of 81 cases were reviewed for similarities. Of these cases, 45 (56%) occurred in male infants and 36 (44%) occurred in female infants. Type A botulinum toxin was responsible for the disease in 47 infants and type B in 34 infants. Mean age of onset was similar in both groups: 12.5 and

10.3 weeks for types A and B, respectively. The reported fatality rate was 3.7%. Data on the consumption of honey before disease onset were available for 59 infants. Twenty-nine (49%) of the infants had been fed honey before botulism onset. No testing of honey samples was performed.

A case-control, prospective study was performed to assess environmental risk factors for infant botulism.⁹ Infant botulism was identified through positive fecal specimens of *C. botulinum* or its toxins submitted to the state laboratory of California from March 1976–June 1978. Two or three controls were selected for each of the documented cases and matched for variables including sex, age, area of residence, and hospital of birth. Study investigators collected epidemiologic data from the homes of infants with documented cases and controls, such as food fed to the infant, soil from the yard, and household vacuum cleaner dust. If the infant had been fed honey and none remained in the home, samples of identical brand, size, and container were purchased from the family's market. Forty-one children with infant botulism were included in the study, with 25 type A botulism cases (63 matched controls) and 16 type B cases (44 matched controls). Forty-three percent of the infants with type B botulism had been fed honey before the onset of illness compared with only 9% of the matched controls ($p=0.005$). No significant difference was found between infants with type A botulism and controls. In addition, six different honey specimens fed to three infants with documented cases contained *C. botulinum*. Ninety honey specimens were analyzed, and nine (10%) tested positive for *C. botulinum*. These samples contained 5–70 *C. botulinum* spores/gram of honey. *Clostridium botulinum* spores also were identified in three soil samples and dust from one vacuum cleaner from the homes of infants with documented cases. The authors concluded that although *C. botulinum* is present in the environment, honey was an identifiable and avoidable source of *C. botulinum* spores and should not be given to infants.

A prospective, case-control study was performed from April 1, 1985, to March 31, 1987, to determine risk factors for infant botulism.¹⁰ The authors sought to identify foods and environmental factors that may contribute to the development of the disease. Sixty-eight infants with laboratory-confirmed cases were included in the study, and each was matched with two control subjects based on date and

hospital of birth. Case patients' and control patients' families were interviewed by phone to obtain the following information: signs of disease; infants' bowel movement patterns; location of residence, defined as city, suburban, rural, or farm; and type and quantity of food exposure before disease onset. Of the 68 infants, 53% were female, 47% were male, and mean age of disease onset was 2 months (range 0.2–11.7 mo). The most common signs of disease were a decrease in bowel movements to less than one bowel movement in a 3-day period (69%) and an altered cry (25%). Case patients were also more likely to have lived in a rural or farm area; however, this difference was not significant compared with the control group. A significantly greater number of infants who tested positive for *C. botulinum* were fed honey before disease onset (16% vs 2% of controls, $p<0.004$). Both type A (5 cases) and type B (6 cases) botulism occurred in infants who had consumed honey. The authors recommended that honey not be fed to infants less than 12 months of age because of the risk of infant botulism.

Honey Consumption and Infant Botulism Outside the United States

In Denmark, a 3-month-old boy was admitted to the hospital secondary to poor feeding, diminished cry, and motor weakness.¹¹ During examination, he was found to have a flaccid facial expression and diminished deep tendon reflexes. Serum obtained 3 days after admission tested positive for *C. botulinum*, and fecal samples tested 1 month later were positive for *C. sporogenes*. The parents reported that the infant had been fed honey for more than 60 days. The honey originated from two sources, one imported and one of Danish origin. Only one of the two samples of honey was available for testing; it was positive for *C. sporogenes*. No *C. botulinum* was isolated from the honey jar. However, the authors noted that *C. botulinum* was isolated from another jar of honey purchased at the same shop as the honey fed to the infant.

An 11-week-old girl was admitted to a hospital in Australia after feeding poorly, increased lethargy, diminished cry, and decreased bowel movements.¹² Examination revealed pooled secretions, weak gag reflex, diminished muscle tone, and decreased spontaneous movements. A culture from the stool was positive for *C. botulinum* and its toxins. History from her parents revealed that the mother had been

dipping the infant's pacifier into a jar of commercially available honey. Subsequent testing of the honey jar was negative for *C. botulinum* toxin or spores.

In Italy, a 9-week-old girl was admitted to the hospital after 10 days of constipation, diminished cry, and lethargy.¹³ She had general hypotonicity and diminished respiratory function. On day 3 of hospitalization, a fecal sample tested positive for *C. botulinum* type B (200,000 spores/gram of stool). The parents reported that they had applied honey to sweeten the infant's pacifier. The honey had originated from three sources, two retail and one home canned. All three samples were available for testing, and the home-canned version tested positive for *C. botulinum* type B.

Clostridium botulinum Spores in Infant Foods

A study in 1978 investigated 55 honey samples from 53 commercial lots and 186 samples from 154 producers to assess the amount of *C. botulinum* spores present in the samples.¹⁴ Of the 241 samples tested, 18 tested positive for *C. botulinum* spores. Two of the commercially available honey samples tested positive, one with type A and the other with type B. The remaining 16 positive samples originated from various honey producers, and the majority were contaminated with type A. The positive samples originated from manufacturers in California, Florida, Iowa, Michigan, Minnesota, Nebraska, Tennessee, and Washington.

In a study 4 years later, 10 categories of infant foods obtained from the Washington, DC, area were tested for *C. botulinum* spores.¹⁵ Infant dry cereals, dry formulas, nonfat dry milk, pasteurized whole cow's milk, canned fruits, fruit juices, honey, corn syrup, granulated cane sugar, and fresh carrots were analyzed. Approximately 95 samples of each of the 10 items from different lots were tested. Two samples of honey tested positive for *C. botulinum* type A. The authors concluded that food processing does not include steps that are lethal to *C. botulinum*; therefore, the organism may be found in some processed food products.

Management of Infant Botulism

Because minimal treatment options are available for infant botulism, management of this illness relies heavily on supportive care. Monitoring and maintaining respiratory function are essential. Approximately 50% of infants

require endotracheal intubation.¹ Nutritional support with enteral feeding is recommended.¹⁻³ The only agent available to treat diagnosed infant botulism is a human-derived botulism antitoxin, also known as botulism-immunoglobulin (BIG).¹⁻⁴ Currently, BIG is obtainable only from the California Department of Health Services under a treatment investigational new drug protocol for types A and B infant botulism.¹⁶ (Physicians may obtain BIG by contacting the study office at 510-540-2646, 24 hrs/day.)

Botulism-immunoglobulin is composed of immunoglobulin G (IgG) antibodies and antitoxins A and B antibodies in sufficient quantities to neutralize circulating levels of botulism neurotoxin.¹⁷ The infant is given one dose of intravenous BIG to help interrupt the neuromuscular blockade caused by *C. botulinum* toxin. The recommended total dose is 50 mg/kg given as a single intravenous infusion. The infusion rate is 25 mg/kg/hour for the first 15 minutes, then 50 mg/kg/hour thereafter (volume not to exceed 75 ml/hr) if no infusion-rate reactions occur. Infusion-related reactions reported with BIG include flushing, chills, fever, back pain, and hypotension. Botulism-immunoglobulin should not be given to patients with selective immunoglobulin A (IgA) deficiency because of the risk of anaphylactic reactions secondary to trace amounts of IgA present in the product.

The efficacy of BIG was assessed in a 5-year placebo-controlled, randomized trial, which showed that infants who received BIG had a significant reduction in hospitalizations and complications.^{1-3, 18} Mean intensive care unit and hospital stays decreased by more than half, from 3.5 weeks to 1.5 weeks and from 5.5 weeks to 2.5 weeks, respectively, in patients treated with BIG ($p<0.05$).¹⁸ In addition, patients treated with BIG had a significant reduction in ventilator days, from 17 to 5 days ($p=0.02$), and a significant reduction in the need for tube feeding, from 10 to 3.5 weeks ($p<0.001$). Treatment with BIG resulted in substantial cost-savings secondary to reduced length of hospital stay, from approximately \$128,000 to \$59,000 ($p<0.001$). Overall, the prognosis for patients with infant botulism is excellent, with a case:fatality ratio of less than 1% for infants hospitalized in the United States.¹⁹

Conclusion

More than 1000 cases of infant botulism have

been reported to the CDC over the past 3 decades. These numbers are alarming because this illness can be fatal if left untreated. Numerous case-control studies and case reports led to the conclusion that consumption of honey by children younger than 12 months old is a positive risk factor for the development of infant botulism. In addition, analyses of honey products showed that approximately 10% of samples tested positive for *C. botulinum* toxin or spores. Clinicians should not recommend honey-containing supplements or the use of honey as a flavoring agent for infants in this age group.

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