

Type F Infant Botulism: Investigation of Recent Clusters and Overview of This Exceedingly Rare Disease

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From 1976 to 2016, neurotoxicogenic *Clostridium baratii* type F caused 18 (<0.5%) reported US infant botulism cases. Six cases occurred during 2012–2013; no common source was identified. Type F infant botulism mostly occurs in very young infants and typically presents more rapidly and severely than illness caused by types A and B botulinum neurotoxin.

Keywords. infant botulism; *Clostridium baratii*; botulinum toxin; clinical spectrum; molecular epidemiology.

Botulism is an acute, flaccid paralytic life-threatening illness caused by *Clostridium* species producing botulinum neurotoxins. Infant botulism (IB), first recognized in 1976, is the most common human form of botulism in the United States. It occurs in infants ≤12 months of age from in situ toxin production due to colonization of the large intestine with neurotoxicogenic *Clostridium* species [1]. The vast majority of IB cases are caused by toxin types A or B produced from *Clostridium botulinum* (<https://www.cdc.gov/botulism/surveillance.html>) [2]. Type F botulism, due to *C. botulinum* or neurotoxicogenic *Clostridium baratii*, is rare among all botulism cases; all US IB type F cases recognized to date for which organism isolation was achieved have been caused by neurotoxicogenic *C. baratii* [1]. The source remains unidentified in most cases; honey is the longest known food vehicle of *C. botulinum* spores to infants, accounting for approximately 5% of cases in recent years [3]. Other linked and suspected sources include chamomile, corn syrup, debris from construction work, dust/soil, pets, powdered infant formula, and untreated well water [4–11]. To date, no environmental reservoir or food source of toxigenic *C. baratii* for IB type F cases has been identified.

Typically, 0–1 toxin type F IB cases occur each year (Figure 1). In 2012 and 2013, 6 geographically dispersed type F IB cases occurred in 2 temporal clusters of 3 cases each, raising concern about a possible common source. To investigate these 6 cases and to better understand the epidemiology of type F IB, we analyzed surveillance data and case reports.

A case of type F IB was defined as stool that contained type F botulinum neurotoxin or type F toxin-producing *Clostridium* species by standard methods [12], from an infant ≤12 months of age, with signs and symptoms consistent with the known paralyzing action of botulinum toxin.

Overview of Surveillance Data and Published Literature

IB has been nationally notifiable since 1983; national surveillance of IB is conducted through reporting of all suspected and confirmed cases to the Centers for Disease Control and Prevention (CDC) and through distribution of the only US Food and Drug Administration (FDA)–approved treatment for types A and B IB, human botulism immune globulin (BIG-IV; BabyBIG), by the California Department of Public Health's Infant Botulism Treatment and Prevention Program (IBTPP) [13]. We reviewed all surveillance data and the literature, via a PubMed search, to identify cases of type F IB during 1976–2016 and ascertain additional epidemiological and clinical findings.

Eighteen type F cases were reported from 10 states: California (3), Colorado (2), Iowa (3), Idaho (1), Massachusetts (1), New Mexico (1), Ohio (3), Texas (1), Virginia (1), Washington (1), and Wisconsin (1). Information available for all cases included infant age at onset, sex, state of residence, month and year of onset, and if the infant was breastfed and/or formula-fed before onset. Eight published reports describing 5 of these type F cases were identified from the literature [14–21]. All were previously captured by national surveillance; no additional type F IB cases were identified by literature review.

Median type F case-patient age at onset was 9 days (range, 2–60 days); 10 (55%) were female. Race was reported for 16 infants, 13 of whom were white. Ten of 12 infants were non-Hispanic. All infants were ≥37 weeks' gestation or described as "term deliveries"; 12 (66%) were born vaginally and 6 by cesarean delivery. One infant in 2004 developed toxic megacolon

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and sepsis as a result of coinfection with *Clostridium difficile* and succumbed to this complication. No seasonality was observed among the 18 cases of type F IB.

The most commonly reported symptoms included weakness, hypotonia, or “floppy baby” (18/18 [100%]), difficulty breathing or dyspnea (16/17 [94%]), weak or altered cry (16/17 [94%]), and difficulty sucking or feeding (15/15 [100%]). Only 7 (41%) infants reportedly experienced constipation before onset. Fifteen of 17 (88%) infants with information available required intubation. Four of 15 (27%) infants received antibiotics before onset, including 2 (13%) who received intravenous antibiotics, 2 (13%) who received erythromycin ophthalmic ointment, and 1 (7%) who received topical antibiotics.

Before illness onset, 1 infant consumed sugar water and apple juice, and 1 infant consumed honey, but none consumed chamomile. One infant (6%) was exclusively breastfed before symptom onset, 4 (22%) received only formula, and 11 (72%) received both breast milk and formula. Two formula brands and 11 formula subvarieties were reported among 15 infants. Ten of 14 (71%) infants with information available had consumed powdered infant formula. For 11 of 16 (69%) infants with information available, exposures to 1 or more environmental factors believed to convey an increased risk for IB were reported, either directly or through a parent’s occupation (eg, construction).

Investigation of 2012 and 2013 Clusters

We developed 2 extensive questionnaires covering patient (n = 1) and birth hospital (n = 1) experiences, which included >250 data fields assessing case-patient information, health status, and pre- and postnatal exposures (eg, nutrition, environmental exposures, infant care products, and medications). Names and lot numbers of commercial products, including formula, were collected whenever possible. Bottle preparation was observed for breast milk and/or infant formula in infant households and birth hospitals. Clinical samples and available leftover powdered infant formula were tested by state health departments or the CDC using standard methods [12]. Isolates from positive clinical samples from the 2012 investigation and 1 isolate from the 2013 investigation were subsequently subtyped at CDC by pulsed-field gel electrophoresis (PFGE) [22]. The FDA collected and tested retained plant samples of powdered infant formula from lots corresponding to leftover powdered infant formula for 2012 cases. For the 2013 investigation, environmental samples were collected by state and local health departments; testing was performed by IBTPP.

Median age at onset for the 6 infants with type F IB in 2012 and 2013 was 9 days (range, 8–21 days), 3 (50%) were girls, and none were low birthweight (median, 3568 g [range, 3310–4337 g]). No geographic clustering characterized the 2012 (Virginia [January], Ohio [February], Massachusetts [March]) or the 2013 (Iowa [June], California [July], Colorado [July]) case patients. Two resided in a city or town, 2 in suburban areas,

and 2 on farms. Three of 6 families reported pets in the home, including cats, dogs, mice, turtles, and geckos.

All 6 cases were caused by neurotoxicogenic *C. baratii*. Two isolates were available for each of the three 2012 patients and 1 isolate from a 2013 patient for PFGE. PFGE patterns across patients were unrelated, while within-patient isolates yielded indistinguishable PFGE patterns. Leftover powdered infant formula was available for 2 of the 2012 cases. The FDA determined that the powdered infant formula lot numbers and production plants differed between the 2 cases. No common ingredients or supplies were used between the production plants. Powdered infant formula collected from infant homes and unopened containers retained by production plants for laboratory testing yielded no growth on culture. Environmental samples, including household dust, air filters, yard soil, and vacuum cleaner contents collected for testing during the 2013 investigation, were negative.

DISCUSSION

Our review of clinical features of US type F IB cases since 1976 supports the characteristic clinical triad of very young age at onset, rapid progression, and severe paralysis [17, 19, 21], as well as a low prevalence of antecedent constipation [23]. These features differ from those of types A and B infant botulism, which typically develop over 1 day to several days, can be mild to severe, entail recovery over weeks to months, and primarily affect infants aged 1–6 months. Because toxin types A and B cause >98% of cases [3] and are generally present in older infants, pediatricians may not consider IB in very young infants presenting with botulism-like symptoms. Clinicians should be aware that human-derived antitoxin BIG-IV (BabyBIG) is licensed only for types A and B infant botulism and is administered on the basis of strong clinical suspicion for IB to maximize treatment efficacy [13]; IB due to other toxin types may be treated with equine-derived heptavalent (A–G) botulism antitoxin obtained from CDC through consultation with the state health department [20, 21].

Similar to most cases of IB, in which the source of exposure is not identified, we found no epidemiologic, laboratory, or environmental evidence to suggest a common exposure for these 2012 and 2013 cases and concluded that the clusters were due either to chance, to increased detection in very young infants by clinicians, to an increase of *C. baratii* type F in the environment, or to another unknown factor.

This report describes the US experience with type F IB and informs public health professionals and clinicians regarding the epidemiological and clinical features of this exceedingly rare disease to improve its recognition and treatment. We recommend continuing education of both clinicians and public health laboratories so they may efficiently and effectively identify and promptly treat cases of type F infant botulism.

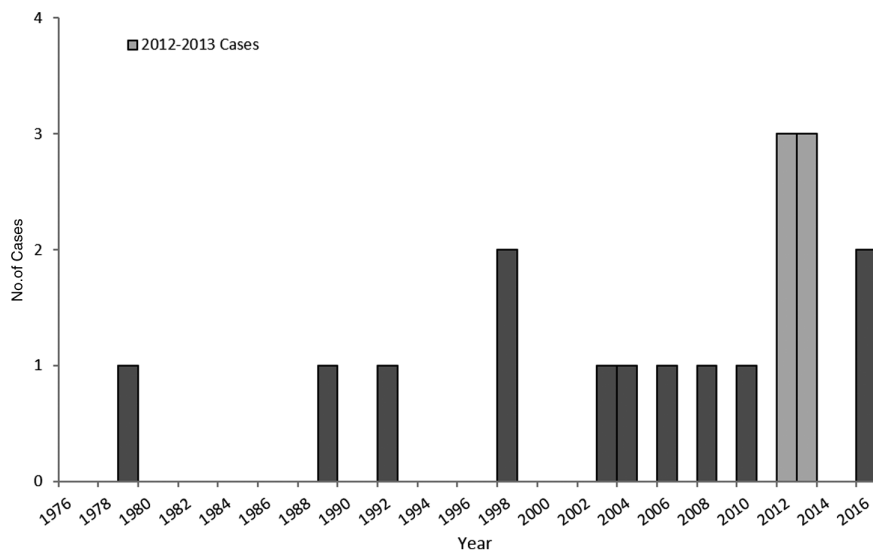


Figure 1. Historic epidemic curve for all type F infant botulism (IB) cases reported, United States, 1976–2016. Before 2012, the historic baseline for type F infant botulism was between zero and 2 cases per year.

Notes

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