CHAPTER 159 – INFANT BOTULISM

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Of the three main forms of human botulism (food-borne, wound, and infant), infant botulism is the most recently recognized (1976) and the most common in the United States and some other countries. Now recognized globally,[55] infant botulism results from a unique pathogenesis. Ingested spores of *Clostridium botulinum* germinate, colonize the infant's colon, and produce botulinum neurotoxin within it. The toxin then is absorbed, binds to peripheral cholinergic synapses, and causes flaccid paralysis. Knowledge of this intestinal pathogenesis resulted in discovery of the novel pathogenic strains *Clostridium baratii* and *Clostridium butyricum*, each of which can produce a botulinum-like neurotoxin and cause the clinical picture of infant botulism. Discovery of these strains enlarged the number of organisms known to cause the "intestinal toxemias of infancy," of which infant botulism is the prototype. Parenthetically, adults and older children rarely may become susceptible to infant-type botulism after broadspectrum antibiotic treatment, intestinal surgery, or inflam-matory bowel disease[6,][28,][38,][62] or in association with a Meckel diverticulum[36,][88] or bone marrow transplantation procedures.[93]

HISTORY

Infant botulism is not a new disease; rather, it has been recognized relatively recently and is an "emerging" infectious disease. The first laboratory-proven case of human infant botulism occurred in California in 1931, although it was misdiagnosed at the time.[15] Decades later and well before the etiology of the disease was apparent, the characteristic clinical features of infant botulism had become evident to discerning observers. In 1974, Grover and associates[43] described nine patients from Pennsylvania with a neurologic syndrome of undetermined cause that from today's perspective almost certainly was infant botulism. The same idiopathic syndrome was recognized in southern California and was reported by Ramseyer and colleagues[85] in 1976 to have a characteristic electromyographic pattern. A year later, Clay and associates[29] linked their eight southern California patients to infant botulism.

The first report of frank botulism in infancy was provided by Pickett and colleagues[84] in 1976. Although the source of botulinum neurotoxin for their two patients was undetermined, the possibility of its in vivo production was suggested.[64,][84] The diagnosis of botulism in these and other California patients was established by identification of *C. botulinum* toxin and organisms in the infants' feces.[64] Evidence also was obtained that ingested spores of *C. botulinum* had produced the toxin in the infants' intestinal tract.[10,][64,][112]

In subsequent years, the clinical spectrum of infant botulism was found to include mild outpatient cases and, in some, but not all[23] locations, sudden unexpected death indistinguishable from typical sudden infant death syndrome.[11,][72,][77,][83] In 1985, a *C. baratii* strain that produced a type F–like botulinum neurotoxin was recognized belatedly as the true cause of a case of infant botulism that occurred in New Mexico in 1979,[44,][48] and in 1986, a *C. butyricum* strain that produced a type E–like botulinum neurotoxin was recognized as the cause of two cases of infant botulism in Rome, Italy.[16] These latter two novel clostridia were discovered only because they caused human infant botulism; their existence suggests that others like them await discovery.

ETIOLOGIC AGENT

C. botulinum is a gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is the soil. Consequently, *C. botulinum* is as ubiquitous as the dust on which it may travel, and, hence, its spores commonly are present on fresh fruits, vegetables, and other agricultural products such as honey. Members of the *C. botulinum* species are so diverse in their biochemical capabilities and nucleic acid profiles that they would not be grouped as a single species except for the similar neurotoxin molecule that each strain produces[47,][97]; at present, the *C. botulinum* species is subdivided into four groups (I to IV) based on metabolic characteristics.[97] Almost all cases of infant botulism in the United States have been caused by group I proteolytic type A or type B strains. Unusual strains of *C. baratii* and *C. butyricum* that make botulinum-like toxins E and F also cause infant botulism.[16,][34,][44,][81,][102,][111] The entire 3.9-megabase (Mb) chromosome and a 16.3-kilobase (kb) plasmid within a *C. botulinum* type A strain were sequenced recently and found to contain 3650 and 19 predicted genes, respectively,[92] thereby launching the era of functional genomic studies of this special bacterium.

In general, each vegetative cell of *C. botulinum* produces just one of seven serologically distinguishable toxins, which arbitrarily have been assigned the letters A to G. Antitoxin raised against one toxin type does not protect against any of the other six types. The different toxin types serve as convenient epidemiologic and clinical markers. Subtypes of several toxin types have been identified by immunologic methods,[56,][106] by neutralization studies using monoclonal antibodies,[3,][98] and by toxin gene nucleic acid investigations.[47] Each toxin molecule is a simple protein consisting of two polypeptide chains of approximately 100,000 (heavy chain) and 50,000 (light chain) daltons joined by a disulfide bond.

Botulinum toxin is the most poisonous substance known.[39] For this reason and because of the ease with which it may be produced, transported, and disseminated, the Centers for Disease Control and Prevention (CDC) has listed botulinum toxin as one of six “category A” (most dangerous) potential bioweapon agents.[13] By extrapolation from studies involving adult primates, the lethal dose in the bloodstream of humans is approximately 1 ng/kg body weight.[13,][39] Its potency for infants may be even higher because of the narrowness of their pharyngeal airway.[109]

The basis of the phenomenal potency of the botulinum (and tetanus) toxins is enzymatic. The light chain of each neurotoxin is a Zn^{2+}-containing protease that hydrolyzes one or more of three intracellular proteins needed for vesicle fusion and release of acetylcholine into the synaptic cleft.[69,][78] The specificity of the toxin for peripheral cholinergic neurons results from their expression of a lower-affinity ganglioside cell surface receptor to which the toxin attaches first, which then is followed by attachment to a second, higher-affinity protein receptor that uniquely appears from the interior of the synaptic vesicle when it fuses with the terminal membrane to release acetylcholine.[27,][51,][79]

PATHOGENESIS

Infant botulism is not the diminutive form of food-borne botulism, and, hence, the disease is not “infantile botulism.” Rather, infant botulism results from a unique infectious disease pathway

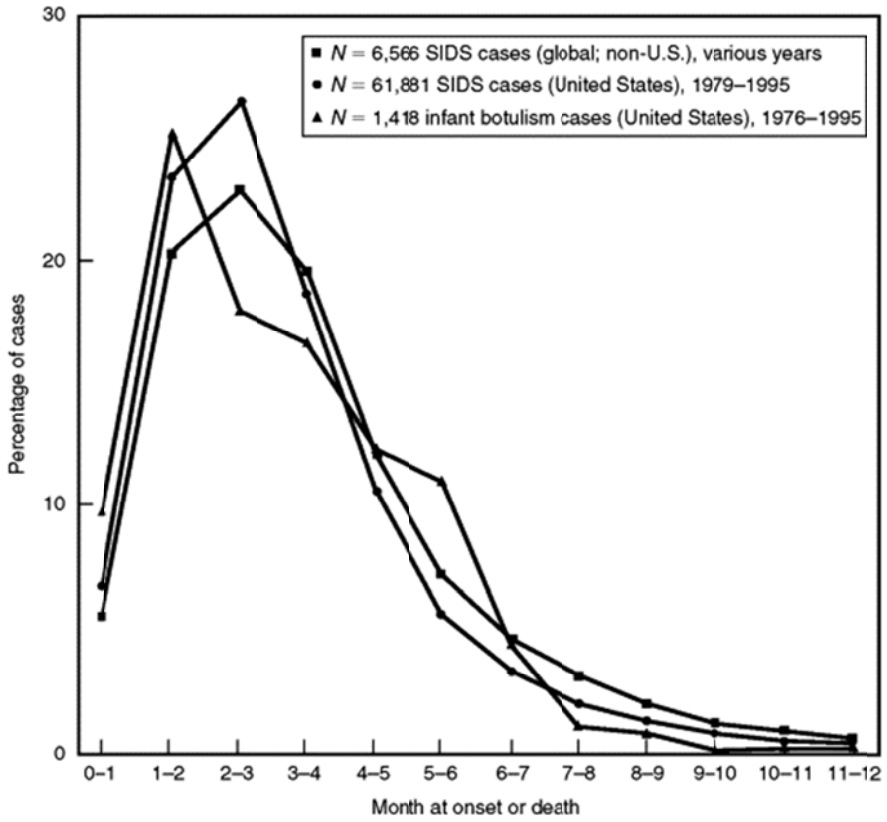
and was so named to emphasize that fact.[10,][64,][112] Ingested spores of *C. botulinum* germinate, colonize the infant's colon, and produce botulinum neurotoxin within it.[10,][45,][66,][68,][112] The toxin subsequently is absorbed and carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly. The light chain then is taken into the cytosol of the neuron, where it blocks the release of acetylcholine by enzymatic cleavage of "fusion complex" proteins.[69,][78] Clinically, the most important of the peripheral cholinergic synapses is the neuromuscular junction; the toxin's action results in flaccid paralysis and hypotonia. Preganglionic cholinergic synapses in the autonomic nervous system also may be affected.[60,][90]

By use of a mouse model system of intestinal colonization (in which the animals paradoxically remained symptom-free), Sugiyama and colleagues[22,][68,][103] have demonstrated that the intestinal microflora of adult animals ordinarily prevents colonization of the gut by *C. botulinum*. Administration of 10^6 type A spores failed to colonize the intestine of normal adult mice, whereas after treatment for 2½ days with a combination of oral erythromycin and kanamycin, half the mice could be colonized by just 2×10^4 spores. When the antibiotic-treated mice were placed in cages with normal mice, they lost their susceptibility to intestinal colonization after 3 days.[22] (Mice normally exhibit coprophagia.) In addition, adult germ-free mice could be colonized intestinally by just 10 *C. botulinum* type A spores. When the germ-free adult animals were placed in a room with conventional mice (but not in the same cages), in 3 days the formerly germ-free animals became resistant to colonization by 10^5 spores.[68]

In contrast to the experimental work with adult mice, normal infant mice were susceptible to intestinal colonization by *C. botulinum* spores.[103] Like human infants, the normal infant mice were subject to colonization for only a limited period (7 to 13 days of age). Susceptibility of the infant mice peaked between days 8 and 11 in a pattern reminiscent of the peaking of susceptibility seen between 2 and 4 months of age in human infant botulism (Fig. 159-1).[8,][103] The infective dose of spores for infant mice was much smaller than that of their antibiotic-treated adult counterparts; the 50 percent infective dose for normal infants was only 700 spores. In one experiment, just 10 spores were needed to colonize an infant mouse.[103] The minimum infective dose of *C. botulinum* spores for human infants is not known, but from exposure to spore-containing honey, it has been estimated to be as low as 10 to 100.[12]

Recognition of the central role of the host's intestinal microflora in determining susceptibility or resistance to colonization by *C. botulinum* has directed attention to factors that may influence the composition of the normal microflora. Diet may be the most important of these factors. When compared with adult-type flora, the infant flora is simpler, with fewer genera and species. The dominant members vary, depending in part on whether the infant is fed only breast milk, only formula milk, or a mixture of the two.[100,][101] In addition, the composition of the intestinal flora is changed if solid foods, such as cereals, become part of the infant's diet. The normal human infant microflora contain several bacterial species, mainly *Bifidobacterium* and *Bacteroides*, that in vitro can inhibit the multiplication of *C. botulinum*.[105]

FIGURE 159 -- 1 Age distribution of infant botulism and sudden infant death syndrome (SIDS)



The onset of infant botulism occurs at a significantly younger age in formula-fed infants (7.6 weeks) than in breast-fed infants (13.7 weeks),[9] perhaps reflecting the earlier availability in formula-fed infants of suitable ecologic niches[9,][60,][100,][101] and the formula-fed infants' lack of the immune factors (e.g., secretory IgA, lactoferrin) contained in human milk.[4,][5,][41] Moreover, introduction of solid foods may "perturb" the intestinal microflora[100] and thereby aid colonization with *C. botulinum*.[4,][8,][60,][99]

An additional physiologic risk factor for infant botulism is slower gut motility, as measured by the frequency of defecation before the onset of illness.[91,][99] Less than one bowel movement per day is a risk factor for both breast-fed and formula-fed infants, but this factor occurred in just 50 percent of cases.[91] Whether a Meckel diverticulum may predispose to the development of infant botulism caused by *C. botulinum*, as it appears to do for infant botulism caused by *C. butyricum*, is not known.[34,][36,][88]

EPIDEMIOLOGY

Any discussion of the epidemiology of infant botulism should be prefaced by the caveat that almost all presently available information is derived from study of only part of the clinical spectrum, namely, hospitalized patients. Accordingly, current perspectives may need to be modified as the outpatient and sudden death portions of the clinical spectrum become defined

more fully. Furthermore, the perceived incidence remains more a reflection of physician awareness and access to diagnostic testing than the actual occurrence of disease. Almost half (41.6%) of U.S. cases have been reported from California, which has the largest number of births of any state. However, California does not have the highest incidence of infant botulism once adjustment is made for differences in annual births (Table 159-1). Notably, 8 of the 11 states with the highest incidence are located west of the Rocky Mountains, and 6 of the 8 are contiguous. The three eastern states with the highest incidence also are contiguous.

TABLE 159-1 -- Cases and Incidence of Infant Botulism. Top 11 States in Incidence, United States, 1977-2005

State	Cases (*N*) 1977-2005	Incidence[*] 1977-2005
Delaware	41	13.4
Hawaii	46	8.6
Utah	92	7.5
California	927	6.3
Pennsylvania	282	6.2
Oregon	47	3.7
Washington	74	3.5
New Jersey	106	3.4
Idaho	17	3.2
New Mexico	24	3.1
Nevada	18	2.8

[*] *Per 100,000 live births per year.*

A unique epidemiologic feature of infant botulism is its age distribution, which, perhaps coincidentally, is virtually identical to the age distribution of sudden infant death syndrome (see Fig. 159-1).[8,][11,][24,][99] Almost all U.S. cases (99.8%) of infant botulism reported to date have occurred in children younger than 1 year old. Some 91.2 percent of cases have occurred in the patients' first 6 months of life, 8.6 percent were distributed over the subsequent 6 months, and just 0.2 percent occurred between 53 and 72 weeks of age. The youngest known patient was just 38 hours old at onset (and had illness caused by *C. baratii* type F toxin),[19] whereas the oldest was 72 weeks old at onset. The illness has occurred in all major racial and ethnic groups and in approximately equal proportions in males and females. A national seasonality is not evident.

Infant botulism has been reported from all inhabited continents except Africa. In the United States, with 28 exceptions (1.1% of cases), all hospitalized cases known as of December 2006 were caused by either type A or type B *C. botulinum* toxin. Forty-nine of the 50 states, representing all regions of the country and including Alaska and Hawaii, now have reported infant botulism. Only Rhode Island has not. In general, the distribution of cases by type of toxin has paralleled the distribution of toxin types in U.S. soil,[96] with type B cases predominating from the great plains eastward and type A cases from the Rocky Mountains westward. The 28

exceptional cases resulted from a variety of toxin types. Two cases in Iowa and one each in California, Ohio, Oregon, New Mexico, Texas, and Wisconsin resulted from a type F–like toxin produced by *C. baratii* strains.[19,][44,][48,][81] Fourteen cases were caused by a *C. botulinum* strain that produced mostly type B and some type A toxin (designated type Ba), and four cases resulted from Bf strains. One case caused by both *C. botulinum* type A and type B from today's perspective probably resulted from either a Ba or Ab strain. Two patients with Bf illness lived in California,[18] one lived in New Mexico, and the fourth patient had traveled there from California immediately before onset of the illness. A fifth type Bf case occurred in England.[95] The only *C. baratii* type F case reported outside the United States occurred in Hungary.[111] In Arizona in 2006, a type E case occurred, but neither *C. butyricum* nor *C. botulinum* could be isolated. All three European *C. butyricum* type E infant botulism cases were reported from Italy, and another in Asia was reported from Japan.[16,][34–36]

As of December 2006, approximately a sixth (516/2932, 17.6%) of all known global infant botulism cases between 1976 and 2006 had been reported from 24 countries other than the United States.[55] Of these cases, Argentina has reported the largest number (366),[61] followed by Australia (32), Canada (27), Italy (23), and Japan (20). The remaining countries have reported only single-digit case occurrence.[55] The non-U.S. cases occurred in countries in Europe (12), Asia (3), the Middle East (3), North America (2), South America (3), and Australia. The small number of reported cases from most non-U.S. countries most likely reflects limited physician awareness of the disease and limited access to specialized diagnostic testing laboratories, as well as actual variation in disease incidence.[55]

Geographic clustering has been noted. In Pennsylvania, 43 of 53 cases in the period 1977 to 1983 occurred in four suburban counties that form an arc bordering the city of Philadelphia.[58] In Colorado, three type A cases occurred in three separate families in a small town with approximately 300 annual births. Two of the infants had used the same crib sequentially; environmental samples, including the crib, soil, and household dust, yielded *C. botulinum* type A.[50] In California, two type A cases occurred 5 years apart in the children of two families who lived one house apart. In another California family, two successive infants each acquired type A infant botulism, but the third child born in sequence did not. Soil and dust specimens from the house where all three infants lived contained *C. botulinum* type A.

The role of breast-feeding and formula-feeding as factors possibly predisposing to illness remains unsettled. All studies to date have identified an association between being breast-fed and being hospitalized for infant botulism.[5,][9,][58–60,][70,][99,][108] This finding has resulted in one perspective that holds that breast-feeding predisposes to the development of illness,[58–60,][99] whereas the other perspective holds that breast-feeding slows its onset sufficiently to permit hospitalization to occur.[4,][5,][8,][9] However, among hospitalized patients in California, the mean age at onset of botulism in formula-fed infants (7.6 weeks) was significantly younger and about half that of breast-fed infants (13.8 weeks). In addition, in California the patients with fulminant-onset infant botulism who stopped breathing and died at home all were formula-fed.[9] The relative susceptibilities of formula-fed and breast-fed infants to infant botulism and the resultant severity of their disease possibly reflect differences in the availability of suitable ecologic niches in the intestinal flora for *C. botulinum*, differences in the availability of immune factors (such as

lactoferrin and secretory IgA) contained in human milk but not in formula milk,[41] or other differences not identified yet.

Probably few, if any, patients with infant botulism acquire *C. botulinum* spores from infant formula, despite isolation in the United Kingdom of *C. botulinum* type B from powdered infant formula consumed by a patient with type B infant botulism.[21,][52] In addition, the possibility that an infant patient may have food-borne botulism needs to be kept in mind because food-borne botulism caused by home-prepared baby food has been recognized.[2]

Honey is the one dietary reservoir of *C. botulinum* spores thus far definitively linked to infant botulism by both laboratory and epidemiologic evidence.[*] More than 35 instances worldwide are known in which *C. botulinum* spores have been found in the actual honey fed to the affected infant before the onset of illness. In each instance, the toxin type (A or B) of the spores in the honey matched the toxin type of the *C. botulinum* that caused the infant's illness; the probability that such perfect concordance occurred by chance is less than 1 in 10 billion. Occasionally, *C. botulinum* has been isolated from honey in which the spore toxin type in the honey did not match the toxin type of the infant's illness[17,][34]; in such instances, the conclusion is that the honey was not the source of the infective spores.

C. botulinum spores have been found in honey from the United States, Argentina, Australia, Canada, China (Taiwan also), Denmark, Finland, Italy, Norway, Spain, Japan, and Central America,[†] but not in honey from the United Kingdom.[20]

In general, only low concentrations *C. botulinum* spores have been found in honey (≤1 spore/g),[65,][74] with the occasional higher concentrations (e.g., 36 to 60 spores/g[74]) thought to result from multiplication of *C. botulinum* in dead bees and bee pupae.[73] Toxin type A, B, C, and F spores all have been found in honey, with some of these toxin types linked to the geographic origin of the honey.[74] For these reasons and because honey is not nutritionally essential, all major pediatric, public health, and honey industry agencies in the United States have joined in the recommendation that honey not be fed to infants. In 2000, several brands of honey sold in the United States began to carry a warning not to feed honey to infants; an equivalent label first appeared on British honey in 1996.

Discussion of the possible role of corn syrup in infant botulism is necessitated by two reports. In 1982, the U.S. Food and Drug Administration (FDA) found *C. botulinum* type B spores in approximately 0.5 percent (5 of 961) of previously unopened retail samples of light and dark corn syrup[54]; the manufacturer then made changes in the production process. In 1989, the federal CDC reported the results of a 2-year epidemiologic study of U.S. cases from all states except California.[80,][99] By subgrouping patients by age and using logistic regression modeling techniques, a statistical association was obtained among the triad of exposure to corn syrup, breast-feeding, and age at onset of 2 months or older.[80,][99]

In contrast to these reports, a 1988 Canadian survey found no *C. botulinum* spores in 43 samples of corn syrup.[46] A 1991 FDA market survey of 783 syrups (354 of which were light corn syrup and 271 were dark corn syrup) concluded that none contained *C. botulinum* spores.[57] A California study (unpublished) of 103 corn syrups, 72 of which had been fed to infants who

subsequently became ill with infant botulism, did not find *C. botulinum* in any sample. Moreover, a 1979 epidemiologic study that simply compared rates of exposure to corn syrup in 41 cases and 107 control infants identified feeding of corn syrup as a significant protective factor against type A infant botulism.[12] The explanation offered for the latter observation was that if a parent chose corn syrup as a sweetener for the infant, the child was unlikely to have been fed honey as a second sweetener. Thus, on the basis of the available evidence, corn syrup appears not to constitute a source of *C. botulinum* spores or a risk factor for the development of infant botulism.

In addition to honey and syrup, hundreds of traditional and nontraditional infant food items, including formula milk, have been examined and found not to contain *C. botulinum*.[63] However, a recent type B infant botulism case in the United Kingdom was traced to *C. botulinum* type B spores in powdered infant formula.[21,][52] Also, in instances not associated with illness, *C. botulinum* spores have been found in raw sugar and molasses but not in refined sugar[75] and in herbal (chamomile) tea and other herbal preparations.[55,][61]

Potential environmental sources of *C. botulinum* spores have been identified in many locales. The soil in Pennsylvania,[60] soil and cistern water in Australia,[71] vacuum cleaner dust in Finland,[77] and the soil and vacuum cleaner dust in California[8] obtained from case homes were found to contain *C. botulinum*, with the toxin type (A or B) in each instance matching that of the ill infant. However, despite the foregoing, it deserves emphasis that for most cases of infant botulism, no source of *C. botulinum* spores ever is identified, even circumstantially. In these cases, illness probably was acquired by swallowing spores adherent to airborne microscopic (invisible) dust.

* See references 8, 12, 17, 46, 49, 54, 65, 85, 87, 88, 104.
† See references 12, 17, 46, 49, 54, 65, 74, 76, 87, 104.

CLINICAL MANIFESTATIONS

Like other infectious diseases, infant botulism displays a spectrum of clinical severity.[4,][8,][11,][59,][60,][83,][90,][108] To date, almost all recognized patients have been sufficiently hypotonic and weak to need hospitalization. Consequently, the present picture of infant botulism is derived from hospitalized patients. However, outpatient cases that displayed only a few days of lethargy, poor feeding, and some decrease in frequency of bowel movement have been detected by alert physicians familiar with the more “classic” illness. At the opposite end of the clinical spectrum are patients whose “catastrophic manifestation” obscured and delayed establishment of the correct diagnosis[67] and those few cases for which the history and clinical findings were indistinguishable from typical cases of sudden infant death syndrome (crib death),[11,][83,][108] approximately 1 in 20 of which (in California) appears to result from fulminant infant botulism.[8,][11]

The onset of infant botulism ranges from the insidious to the abrupt. At one extreme are patients who were nursing normally 6 hours before becoming so floppy that acute meningitis was the diagnosis at initial evaluation, and at the other extreme are patients who returned to their physicians four times in a week as the signs of illness gradually became apparent. Though rare,

illness caused by *C. baratii* type F appears to be characterized by the triad of very young age at onset, rapid onset, and profound paralysis.[19,][81] Equally rare, illness caused by *C. butyricum* type E may be manifested as a paradoxically rigid abdomen and associated bowel colonization with *Clostridium difficile*.[34,][35]

In the "classic" case of infant botulism, the first sign of illness almost always is constipation (defined as 3 or more days without defecation in a previously regular infant), yet the constipation often is overlooked. A few patients (<5%) will not have a history of constipation. Usually, a mother first notices listlessness, lethargy, and poor feeding, together with breast engorgement if the infant had been nursing. The increasing weakness over the ensuing 1 to 4 days typically brings the baby to medical attention.

Botulism is manifested clinically as a symmetric, descending paralysis. Early in the course, weakness and hypotonia characterize the illness, and the remainder of the physical examination not involving the neuromuscular system is normal. The first signs of illness are found in the cranial nerves; one cannot have infant botulism without having bulbar palsies. The typical patient has an expressionless face, a feeble cry, ptosis (evident when the eyelids must work against gravity), poor head control, and generalized weakness and hypotonia (Fig. 159-2). Eye muscle paralysis varies, and the pupils often are midposition and initially briskly reactive (Table 159-2). The gag, suck, and swallow reflexes are impaired, as is the corneal reflex if it is tested repetitively. Deep tendon reflexes frequently are normal at initial evaluation and diminish subsequently as the paralysis extends and increases. The "frog's legs" sign often is seen. Patients are afebrile unless a secondary infection (e.g., aspiration pneumonia) is present.

Figure 159-2 – Mildly affected, 7-week-old infant with botulism. Note the minimal signs, including ptosis, mildly disconjugate gaze, expressionless face, slack jaw, and neck and arm hypotonia

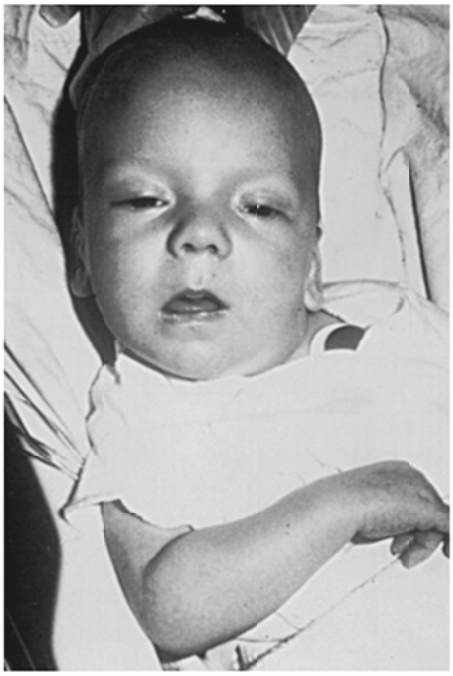


TABLE 159-2 -- Neurologic Signs Helpful in the Diagnosis of Infant Botulism

1.	Take the patient to a dark room. Shine a bright light into the eye; note the quickness of pupillary constriction. Remove the light when the constriction is maximal; let the pupil dilate again. Then immediately repeat the light, continuing thus for 1 to 3 minutes. The initially brisk pupillary response may become sluggish and the pupil unable to constrict maximally. (Fatigability with repetitive muscle contraction is the clinical hallmark of botulism.)
2.	Shine a bright light onto the fovea and keep it there for 1 to 3 minutes, even if the infant tries to deviate the eyes. Latent ophthalmoplegia may be elicited, purposeful efforts to avoid the light may diminish, or both.
3.	Place a clean fifth finger in the infant's mouth while taking care to not obstruct the airway. Note the strength and duration of the reflex sucking. The suck is weak and poorly sustained. The gag reflex strength also may be quickly checked (if the infant has not been fed recently).

Adapted from Arnon, S. S.: Infant botulism. Annu. Rev. Med. 31:541-560, 1980. Reproduced with permission from Annual Reviews, Inc.

The results of most laboratory and clinical studies are normal. At admission, the child may have evidence of mild dehydration and fat mobilization because of diminished oral intake. Occasionally at admission, the protein concentration in cerebrospinal fluid (CSF) becomes elevated because of the mild dehydration. If infant botulism is suspected soon after the child is admitted, electroencephalography, computed tomography, and magnetic resonance imaging seldom are required, but if performed, these examinations yield nonspecific or normal results. Electromyography may offer rapid bedside confirmation of the clinical diagnosis (see "Differential Diagnosis and Diagnosis").[30,][33]

Small amounts (<5 mouse LD_{50}/mL) of botulinum toxin sometimes can be identified in serum specimens if they are collected early in the course of the illness.[16,][34,][45,][61,][82,][107,][110] In one U.S. report, almost one patient in eight had toxin demonstrable in serum.[45] The definitively diagnostic laboratory study is examination of feces for the presence of *C. botulinum* organisms and toxin, which is the only certain way to identify the neurotoxin type (A, B, or other) responsible for the illness. Clinically suspected cases that lack an identified toxin type not are included in official tallies of infant botulism.[25,][26,][55]

The usual hospital course of untreated infant botulism has certain general features.[4,][53,][60,][90] After the increasing weakness has necessitated admission, the weakness and hypotonia continue to progress and usually become generalized. The deep tendon reflexes, which may be normal at admission, may diminish or disappear temporarily. The nadir of paresis and paralysis in untreated patients usually occurs within 1 to 2 weeks after admission; such patients often remain at their nadir for as long as 1 to 3 weeks before showing signs of improvement. However, once strength and tone begin to return, the improvement continues steadily and gradually over the ensuing weeks in the absence of complications (Table 159-3). In contrast, patients treated with human botulism immune globulin have a mean hospital stay of approximately 2 weeks (see "Treatment").[14]

In the California experience, infant botulism does not have a relapsing or biphasic course, and perceived "relapses" have been found, in retrospect, to be an indication either of the onset of a complication (see Table 159-3) or of premature discharge. However, the clinical experience elsewhere with regard to relapses has been different.[34,][40,][86,][90] The patient is ready for discharge when gag, suck, and swallow are sufficiently strong both to protect the airway against accidental aspiration and to ensure adequacy of oral intake. Parents also may be taught to feed by gavage at home. In either situation, discharge may occur safely while head lag and constipation still are present.

TABLE 159-3 -- Complications of Infant Botulism

Adult respiratory distress syndrome
Anemia
Aspiration
Blood pressure instability
Clostridium difficile colitis
Fracture of the femur and humerus
Inappropriate secretion of antidiuretic hormone
Misplaced or plugged endotracheal tube
Necrotizing enterocolitis
Otitis media
Pneumonia
Recurrent atelectasis
Respiratory arrest
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tension pneumothorax
Tracheal granuloma
Tracheal stenosis
Tracheitis
Tracheomalacia
Transfusion reaction
Urinary tract infection

DIFFERENTIAL DIAGNOSIS AND DIAGNOSIS

When initially brought to medical attention, patients with infant botulism often are so mildly weak and hypotonic that the illness is not considered. Even today, more than 30 years after the disease first was recognized, suspected sepsis remains the most common admission diagnosis for patients with infant botulism. A careful history (constipation commonly is overlooked) and physical examination (especially cranial nerve function) usually can identify patients with infant

botulism correctly and render unnecessary most additional testing for the other entities typically suspected (Table 159-4). A review of entities that so closely mimicked infant botulism that botulism immune globulin was administered soon after admission identified spinal muscular atrophy type I, mitochondrial disorders, and a small number of other conditions as the actual diagnoses (Table 159-4).[37]

The diagnosis of infant botulism is established by identification of *C. botulinum* organisms in the feces of an infant with clinical signs consistent with the paralyzing action of botulinum toxin.[25,][53,][64] Extensive studies have demonstrated that *C. botulinum* is not part of the normal resident flora of infants or adults.[8,][45,][100,][101] If the fecal specimen is obtained sufficiently early in the course of the illness, it also will contain botulinum toxin. Because of the patient's constipation, an enema with sterile, nonbacteriostatic water (not saline) commonly is needed to obtain a fecal specimen for diagnostic examination. The mouse neutralization test remains the most sensitive and specific assay for botulinum toxin.[26] Laboratory diagnosis that identifies the type of toxin responsible for the illness is essential for the case to be registered as infant botulism[55] and is important in determining the prognosis; mean hospital stay is significantly longer in untreated type A cases than in untreated type B cases (see "Treatment").[4,][14] Physicians are reminded that in most states, botulism or suspected botulism (all types) is an immediately reportable illness.

TABLE 159-4 -- Working Differential Diagnosis of Infant Botulism

Admission Diagnoses	Subsequent Working Diagnoses	Clinical Mimics*
Rule out sepsis	Hypothyroidism	Spinal muscular atrophy type I
Dehydration	Metabolic encephalopathy	Mitochondrial disorders
Viral syndrome	Amino acid metabolic disorder	Metabolic and amino acid disorders
Pneumonia	Heavy metal poisoning (Pb, Mg, As)	Assorted infectious disease disorders
Idiopathic hypotonia	Drug ingestion	Miscellaneous, including central nervous system disease
Failure to thrive	Poliomyelitis	Probable infant botulism lacking laboratory verification
	Brain stem encephalitis	
	Myasthenia gravis	
	Viral polyneuritis	
	Guillain-Barré syndrome	
	Hirschsprung disease	
	Werdnig-Hoffmann disease	

**Patients so indistinguishable from infant botulism at admission that they were treated with human botulism immune globulin intravenous (BIG-IV). From Francisco, AM. O., and Arnon, S. S.: Clinical mimics of infant botulism. Pediatrics* 119*:826-828, 2007.*

At the bedside, electromyography sometimes can be helpful in ambiguous situations in that when a clinically weak muscle is tested, electromyography often discloses a pattern known by the acronym BSAP (brief, small, abundant motor unit potentials).[10,][30,][33,][42,][90,][94] The edrophonium (Tensilon) test is unnecessary because congenital myasthenia gravis can be

excluded by the history and de novo myasthenia does not occur at this age because of the immaturity of an infant's immune system. Likewise, Guillain-Barré syndrome, which is well-documented by finding a consistently elevated protein concentration in CSF, is of negligible occurrence in infancy. In infant botulism the protein concentration in CSF is normal, an occasional exception being that of a specimen collected while the child is mildly dehydrated.

TREATMENT

Specific therapy for infant botulism is now available. In California, a 5-year, randomized, double-blinded, placebo-controlled treatment trial demonstrated the safety and efficacy of human-derived botulinum antitoxin, known formally as human botulism immune globulin intravenous (BIG-IV).[7,][14] Use of BIG-IV reduced mean hospital stay per case from approximately 5.5 weeks to approximately 2.5 weeks ($p < 0.001$) and reduced mean hospitalization cost per case by about $90,000 (2004 dollars; $p < 0.001$). In a 6-year, follow-on, open-label study, treatment with BIG-IV within 7 days of hospital admission reduced mean hospital stay to 2.2 weeks. Treatment with BIG-IV should be started as early in the illness as possible to maximally neutralize the toxemia and should not be delayed for laboratory confirmation of the clinical diagnosis. BIG-IV may be obtained from the California Department of Public Health as a public service orphan drug (24-hour telephone: 510-231-7600; website: *www.infantbotulism.org*).

Successful management of infant botulism also depends on meticulous supportive care and the anticipation and avoidance of potentially fatal complications (see Table 159-3). Feeding and breathing generally require the most attention. At admission, patients should receive cardiac, respiratory, and transcutaneous blood gas monitoring (especially carbon dioxide pressure) until it is clear that the paralysis no longer is progressing. An endotracheal tube often is necessary to maintain and protect the airway, even in the absence of a need for mechanical ventilation. Particular care should be taken to avoid transmission of nosocomially acquired *C. difficile* colitis.[35,][89]

A third cornerstone of management is forbearance. Antibiotics should be reserved to treat the principal secondary infections (pneumonia, urinary tract infection, otitis media) because their use may result in lysis of intraintestinal *C. botulinum* with liberation of intracellular neurotoxin into the gut lumen and absorption. This potential problem may be avoided by prompt use of BIG-IV because its long (28-day) half-life and substantial antitoxin content enable it to neutralize all absorbed and circulating toxin.

Tracheostomy is not necessary.[1] Improved management of the airway can be accomplished by two simple positioning measures. First, for expansion of the thoracic cage and assistance in diaphragmatic function, patients should be placed in an older-style crib, the rigid bottom mattress of which can be lifted to elevate the entire body to a 30-degree angle. Second, to tip the head back and to maintain normal curvature of neck and airway, a soft cloth should be rolled to the thickness of about three fingers and placed under just the child's neck. This maneuver allows oral secretions to drain away from the trachea and into the true posterior pharynx, where they are swallowed most easily.

Intravenous feeding (hyperalimentation) is discouraged because of its potential for secondary infection and because of the success obtained with nasogastric or nasojejunal tube feeding. Mother's milk is the nutritional fluid of choice. Isolation measures or “enteric precautions” are not required, but meticulous handwashing is. Soiled diapers should be autoclaved because they can be expected to contain botulinum neurotoxin as well as viable spores and vegetative cells of *C. botulinum*. For this reason, staff with open lesions on their hands should not handle the diapers.

In the untreated (placebo) group in the 5-year, randomized clinical trial of BIG-IV, when compared with the untreated type B patients, the untreated type A patients had significantly longer mean hospital stays (6.7 versus 4.2 weeks), mean stays in the intensive care unit (ICU) (6.5 versus 3.1 weeks), and mean time on a ventilator (6.4 versus 2.2 weeks).[14] However, the distributions of the untreated type A and type B patients partially overlapped for all three parameters. Hence, untreated illness caused by type A toxin appears to be generally, but not invariably more severe than that caused by type B toxin. With use of BIG-IV, the mean duration of hospital stay has been reduced to approximately 2.2 weeks for both type A and type B patients, with comparable decreases also in the duration of stay in the ICU and time on a ventilator.[14]

OUTCOME AND PROGNOSIS

Recovery from infant botulism occurs through regeneration of the poisoned terminal unmyelinated nerve endings. The newly synthesized nerve twigs then induce the formation of new motor end-plates that are indistinguishable functionally and morphologically from the original ones.[31,][32] In experimental animals and in human infants, completion of this process takes several weeks.[32] Consequently, in the absence of hypoxic cerebral complications, full and complete recovery of strength and tone is the expected outcome of infant botulism. In addition, because botulinum toxin does not cross the blood-brain barrier to any functional degree, the child's intelligence and personality remain intact. Parents often need reassurance on this latter point. Re-infection with the same or a different toxin type of *C. botulinum* has not occurred. In the United States, the case-fatality ratio of hospitalized patients is less than 1 percent, a reflection of, and tribute to, the high quality of intensive care given to these critically ill infants. In other countries, the experience has not been as fortunate.[55]

PREVENTION

At present, the one known way to prevent infant botulism is not to feed honey to infants, and all major pediatric and public health agencies have endorsed this recommendation. Breast-feeding may help moderate the rapidity of onset and the severity of illness. Persuasive evidence that links infant botulism to the ingestion of corn or other syrup is lacking. In the pre–BIG-IV era, the patient with the most protracted illness was hospitalized for 10 months in 1988 at a cost of more than $1,000,000 (2004 dollars). Mean hospital cost for the placebo-treated patients in the 1992 to 1997 randomized clinical trial of BIG-IV was $163,400, which was reduced in the BIG-IV group to $74,800, a net cost-savings of $88,600 (2004 dollars).[14] These economic facts combine with humanitarian considerations to make a compelling case for the prevention and effective treatment of infant botulism.

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