Botulism

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Practice Gap

Prompt clinical identification of botulism is vital to provide timely therapy to improve patients' outcomes.

Objectives

After completing this article, the reader should be able to:

1. Recognize signs and symptoms of botulism and its different clinical syndromes.
2. Understand the mode of acquisition of botulism and preventive measures.
3. Understand the epidemiology, risk factors, and management of botulism.
4. Become familiar with the resources to obtain diagnostic aid and antitoxin, when indicated.

AUTHOR DISCLOSURE Dr Carrillo-Marquez has disclosed no financial relationships relevant to this article. This commentary does not contain discussion of an unapproved/investigative use of a commercial product or device.

INTRODUCTION

Botulism is a rare, severe, and potentially lethal condition caused by the botulinum toxin. It is characterized by symmetric cranial nerve palsy, commonly followed by symmetric, descending, flaccid paralysis of involuntary muscles, which may result in respiratory compromise and death. (1) The sensorium remains intact because the botulism toxin does not cross the blood-brain barrier. (2) Fever is notoriously absent, except in cases complicated with secondary nosocomial infections. (3)

The botulinum toxin, which is recognized as one of the most potent neurotoxins, is produced by a few clostridial species but most commonly by *Clostridium botulinum*.

There are 4 recognized clinical syndromes: foodborne botulism, wound botulism, infant botulism, and intestinal toxemia. Inhalational botulism could result from aerosolization of botulinum toxin, but it does not occur naturally and has been associated with potential bioterrorism. Iatrogenic botulism can result from injection of the toxin. (1)(4)(5) All forms of botulism exhibit the same distinct neurologic syndrome of symmetric cranial nerve palsy followed by symmetric flaccid paralysis of voluntary muscles with subsequent respiratory compromise.

The mainstays of treatment are early diagnosis, intensive supportive care, and timely botulinum antitoxin administration. As a rare condition, botulism may be

challenging for the clinician to recognize, particularly early in its course. Because botulism is potentially fatal, it is important for clinicians to become familiar with the clinical manifestations to diagnose, treat, and report the disease to public health authorities.

ETIOLOGY

C botulinum is a Gram-positive, strict anaerobic, spore-forming organism that is ubiquitous in soil, dust, and aquatic sediments worldwide. The botulinum toxin is produced by several clostridial species, most commonly *C botulinum. C baratii, C butyricum, and C argentinense* have also been associated with botulism and botulinum toxin production. (6)(7)(8)

Botulism is caused by the effects of the botulinum toxin present in the circulation after its absorption from a wound or other mucosal surfaces. The botulinum toxin is regarded as the most potent neurotoxin known. (9) The estimated lethal dose for humans, extrapolated from studies on primates, is 0.09 to 0.15 μg intravenously, 0.80 to 0.90 μg by inhalation, and 70 μg orally. (10)(11) Because a mouse bioassay is the standard method of detection and quantification of the toxin, its biologic activity is expressed in terms of mouse intraperitoneal lethal dose (MIPLD50). (1) One mouse unit is defined as the intraperitoneally injected quantity of botulinum toxin required to kill 50% (LD50) of an experimental group of mice, each weighing 20 g. The lethal dose of the onabotulinumtoxinA preparation for a person of 70 kg is calculated to be 2,500 to 3,000 units (approximately 100 times the typical dose for cosmetic purposes and 6 times the dose for treatment of muscle movement disorders).

The remarkable toxicity of botulinum toxin has garnered attention as a possible agent in bioterrorism and biologic warfare. (10)

Seven antigenic toxin types of *C botulinum* have been identified and designated by the letters A through G. Human botulism is caused more commonly by neurotoxins A, B, and E and rarely by toxin F. (1)(6)(8) The toxins are large, single polypeptides of similar structure. They cause flaccid paralysis by blocking acetylcholine transmission across the neuromuscular junction at the presynaptic motor-neuron terminal. (12) Due to its large size (150 kDa), the toxin does not cross the blood-brain barrier. (2)

The neurotoxin is heat labile and can be destroyed with exposure at 80°C for 30 minutes or at 100°C for 5 minutes. Toxin is produced by *C botulinum* during active growth, which occurs at temperatures of 3°C to 48°C and pHs of 4.8 to 8.5, and it is released during bacterial lysis. The toxin is unstable at pH values higher than 7. If the organism is present in acidic food, improper processing can permit toxin production. (6)

Under stress caused by hostile growth environments (eg, suboptimal pH, temperature), *C botulinum* forms spores that resist standard cooking and food processing measures. The spores can withstand boiling for long periods of time (100°C for >5.5 hours) but can be destroyed at 116°C for 10 minutes or at 121°C for a few minutes.

The spores can germinate, grow, and release the potent neurotoxin in foods under anaerobic conditions. However, the combination of conditions required for spore germination, namely, anaerobic milieu, nonacidic pH, and low salt and sugar content, is rarely achieved in food, although it could be present in inappropriately handled home-canned vegetables and fermented fish, which are the most commonly identified sources of foodborne botulism, and explains the small number of cases. (4) Modern industrial canning techniques and educational resources have been developed for safe home food canning and the killing of *C botulinum* spores. (13)

EPIDEMIOLOGY AND TRANSMISSION

Botulism is a rare disease that occurs naturally worldwide. (14) Approximately 110 cases are reported per year in the United States. (15)

Since 1973, the Centers for Disease Control and Prevention (CDC), in partnership with the Council of State and Territorial Epidemiologists, has maintained a National Botulism Surveillance System to collect demographic, clinical, and epidemiologic data of all laboratory-confirmed botulism cases in the United States, including continuous monitoring for detection of outbreaks. Cases must meet the established case definition of botulism. (16) All cases are grouped within foodborne, wound, infant, and "other" categories. The latter encompasses cases where the transmission route is unknown, is iatrogenic, or is due to adult intestinal botulism. (15)(16)

Because the CDC, Alaska Department of Public Health, and California Department of Public Health are the only suppliers of botulism antitoxin in the United States, all or almost all recognized cases of botulism are recorded. However, underreporting cannot be excluded; some cases might be unrecognized or misdiagnosed and people with mild symptoms might not seek medical attention. (17)(18)(19)

Foodborne Botulism

Approximately 15% of the annually reported cases of botulism in the United States correspond to foodborne botulism. (15) The annual average was 17 cases from 2006 through

2010. (8) Men and women are equally affected. Mean age of infected people is 53 years (range, 3–91 years). (8)(15)

The previously cited requirements for spore germination make inappropriately handled home-canned or raw fermented foods the primary sources of infection. They provide the environment for germination of *C botulinum* spores and botulinum toxin production in food. When the contaminated food is eaten, the preformed toxin is ingested, absorbed through the gastrointestinal tract into the bloodstream, and transported to the neuromuscular junction, where it blocks neurotransmitter release and creates the ensuing flaccid paralysis. Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, might precede the typical neurologic manifestations. The incubation period is 12 to 48 hours (range, 6 hours–8 days) following ingestion of contaminated food. (8)

According to the CDC, botulism cases have been reported in 46 states, Puerto Rico, and Washington, DC. However, more than 50% of all the foodborne outbreaks since 1950 have been reported from California, Washington, Colorado, Oregon, and Alaska. (15) Botulism is a public health concern in Alaska, where the majority of cases have been associated with improper handling and storage of Alaska native foods.

In the United States, toxin A has been responsible for approximately 50% of the reported foodborne cases. Toxins B and E account for 25% each. Type E toxin is mostly found in association with fish and fish products whereas type A and B might be related to other types of food.

Type A is primarily reported from the western states, whereas type B is seen more frequently in the eastern states. Type E outbreaks occur more commonly in Alaska and the Great Lakes region. (6) There is no person-to-person transmission, but small outbreaks have been reported among individuals exposed to the same home-processed food. The latter source accounts for most reported outbreaks. (15) There is potential for development of larger outbreaks when associated with foods prepared at restaurants or commercially, situations that have been increasingly reported. (20)

The most common reported food sources are vegetables, fish, fruits, and condiments. Foods associated with botulism cases include traditional Alaskan native foods (fermented fish dishes), (21) baked potatoes, (18) potato salad, (22) potato soup, (23) chopped garlic, home-canned vegetables (ie, green beans, green bean and carrot blend, asparagus), (21) sautéed onions served by restaurants, and commercial frozen pot pie mishandled at home. (6)

Other small botulism outbreaks have been reported in association with illicit production and consumption of "pruno" in prisons in California, Utah, and Arizona. Pruno is an alcoholic fermented beverage that is produced illegally by inmates using different ingredients but most commonly fruit, fruit juices, sugar, ketchup, and potatoes. (24)(25)(26)

Infant Botulism

Infant botulism develops when ingested *C botulinum* (or related toxigenic species) spores germinate and produce botulinum toxin in the gastrointestinal tracts of infants. (3)(8) This phenomenon is believed to occur through a mechanism of transient permissiveness by the intestinal microflora; the conditions of the normal human intestine are not favorable for germination of the spores or toxin production. *C botulinum* spores might be accidentally ingested without consequence by adults. An exception to this are the adult cases of intestinal toxemic botulism, which have the same pathophysiology as infant botulism but occur in older children and adults who have predisposing gastrointestinal factors, such as intestinal surgery, exposure to antibiotics, or underlying gastrointestinal disorders. (27)(28)(29)

Infant botulism has been reported from all inhabited continents except Africa, with variable rates possibly influenced by cultural feeding practices, soil characteristics, and disease awareness and surveillance as well as reporting capabilities. Infant botulism is the most commonly reported form of botulism in the United States, accounting for approximately 70% of the reported cases, with an annual average of 90 laboratory-confirmed cases between 2006 and 2010, age range of less than 1 to 60 weeks (median age, 16 weeks), and a 1:1 male-to-female ratio. (8) There is no person-to-person transmission. Because the disease is rare and sporadic, it has no epidemic potential. However, according to the CDC, clustering of cases has been noted in some suburban areas in the eastern United States and some small towns and rural areas in the western states. (13)(15)(19)

Although most infant botulism cases have been reported in California (~39%), the higher number of births in this state makes the actual incidence similar to eastern states. Of note, 8 of the 11 states with the highest incidences are located west of the Rocky Mountains, and 6 of the 8 are contiguous. (3) The 5 states with the highest incidences of infant botulism between 1977 and 2005 were Delaware, Hawaii, Utah, California, and Pennsylvania, with incidences of 13.4, 8.6, 7.5, 6.3, and 6.2 per 100,000 live births per year, respectively. (3)

Almost all hospitalized cases of infant botulism in the United States (98.6%) as of 2011 were caused by either type A or type B *C botulinum* toxin. (3)

Because *C botulinum* is ubiquitous in soil and dust, its spores can be found in a wide variety of fresh and cooked agricultural products, including fruits, vegetables, and honey.

A definitive association with consumption of honey has been found in approximately 20% of infant botulism cases.

(1) This is the only dietary modifiable risk factor proven to date. Also, 99.7% of the cases reported in the United States have been reported in children younger than age 1 year. These facts led to the recommendation of avoiding feeding honey to infants younger than age 12 months, which is supported by every major pediatric and public health organization as well as honey manufacturers. (3)(8)(30)

No cases of infant botulism have been proven, thus far, to be related to consumption of light or dark corn syrup. However, their manufacturers cannot ensure that any of these products is free of *C botulinum* spores at any given time. (8)

Affected infants are typically previously healthy and the only person affected in the household. Other than honey consumption, risk factors for most cases remain unclear. Exposure to environmental sources of *C botulinum,* such as vacuum cleaner dust, soil, and nearby building construction, have been noted in some cases, but case-control studies evaluating these factors are not available.

Infant botulism has a variable clinical spectrum, ranging from mild signs and symptoms to sudden death and insidious or fulminant onset. Most of the epidemiologic data have been derived from hospitalized cases.

The role of breastfeeding remains controversial, with most studies finding an association between breastfeeding and hospitalization. However, the onset of the illness was at a significantly younger age in formula-fed infants (7.6 weeks) compared to breastfed infants (13.7 weeks), and patients who presented with fulminant infant botulism were all formula-fed. (31) These findings have been interpreted as suggesting that breastfeeding might slow the onset of infant botulism sufficiently to allow hospitalization rather than represent a predisposition for development of the illness.

The incubation period of infant botulism is between 3 and 30 days from the time of exposure to the spore-containing material. (8)

Wound Botulism

Wound botulism occurs when devitalized or traumatized tissue becomes contaminated by clostridial spores, which germinate and produce the toxin in the wound. Wound botulism is usually associated with wound abscesses. Of the botulism cases reported annually in the United States, approximately 30% to 40% are due to wound botulism. From 2006 through 2010, 26 laboratory-confirmed cases were reported annually on average. (8) The median age of affected patients is 41 years, with a range of 23 to 58 years. (15) In the United States, approximately 80% of cases are caused by toxin A and 20% by toxin B. (20)

Before 1980, the majority of those affected were female; since then, 60% of the cases reported were in males, primarily associated with injection of black tar heroin. This trend was observed through the 1980s and 1990s in California and other western states where virtually all the cases have been reported. (15)

In recent years, most new cases have occurred in users of contaminated injectable black tar heroin associated with needle puncture sites, (20) although rare cases have been associated with nasal or sinus lesions resulting from chronic cocaine use. (32)(33) Before this trend, crush injury and devitalized tissue were risk factors for wound botulism, noted most commonly in male children and adolescents with compound extremity fractures. There is no person-to-person transmission. The incubation period is 4 to 14 days from time of injury until onset of symptoms. (8)

CLINICAL MANIFESTATIONS

The clinical hallmark of botulism is symmetric descending acute flaccid paralysis (AFP) that can progress to respiratory compromise. Multiple symmetric bulbar paralyses appear first. Bulbar relates to the lower brainstem area or medulla oblongata, which controls cranial nerves VII through XII, but the term is used regardless of the level of the lesion (muscle, neuromuscular junction, peripheral nerves, or motor nuclei). The terms paralysis or palsy are used to describe weakness. Bulbar paralysis results from diseases affecting those nerves or the area that controls them; the paralysis manifests as weakness of facial muscles and speech and swallowing deficits. Clinical manifestations include ptosis, blurred vision, diplopia, dysphagia, and decreased gag and corneal reflexes. In infants, poor feeding, lack of facial expression, weak suck, feeble cry, and even obstructive apnea due to tongue floppiness initially might not be recognized as bulbar in origin. (6) Generalized weakness, hypotonia, and poor head control are also observed in affected infants.

All forms of botulism present essentially with the characteristic neurologic syndrome. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea might be present in foodborne botulism but are not described in any of the other forms. The exception is constipation, which is regarded as a heralding sign of infant botulism and can be present in all forms of botulism. Constipation usually precedes paralysis but is frequently overlooked.

Visual complains and difficulty swallowing are common initial signs. Autonomic dysfunction manifesting as decreased tearing and salivation are commonly unrecognized and misinterpreted as dehydration. Blood pressure and

heart rate might fluctuate. Decreased intestinal motility, poor anal sphincter tone, and bladder atony are common. Respiratory difficulty is usually not present at the time of admission, but its presence varies, depending on the patient's age and promptness of the diagnosis. Without treatment, respiratory paralysis and death might occur.

Characteristically, the sensorium remains intact because the toxin does not cross the blood-brain barrier.

Fever is typically absent and might be an indication of a secondary bacterial infection or associated with wound infection or abscess formation in cases of wound botulism. Fever has been described, however, in wound botulism, although the wound itself might not show evidence of infection.

The clinical spectrum of infant botulism is wide and ranges from mild disease to sudden death with an insidious or fulminant onset. In "classic" infant botulism, fatigability after repeated assessment is pathognomonic and should be assessed during a thorough physical examination. Signs of "fatigue" include extraocular muscle paralysis and decreased papillary, gag, suck, and swallow reflexes. Deep tendon reflexes might be normal on initial assessment but could diminish with progression of the paralysis. "Frog's legs" sign is often noted. Patients appear "floppy" due to generalized hypotonia and weakness. Other signs include poor head control, feeble cry, expressionless face, and ptosis (noticeable when the eyelids must work against gravity). (3) The Table summarizes the reported frequencies of signs and symptoms of foodborne and wound botulism compared with infant botulism. (6)(34)

TABLE. **Frequencies of the Most Common Signs and Symptoms of Foodborne and Wound Botulism Versus Infant Botulism**

	FOODBORNE AND WOUND BOTULISM	INFANT BOTULISM
Symptoms	Dysphagia: 96% Dry mouth: 93% Diplopia: 91% Dysarthria: 84% Fatigue: 77% Upper extremity weakness: 73% Constipation: 73% Lower extremity weakness: 69% Blurred vision: 65% Nausea: 64% Dyspnea: 60% Vomiting: 59% Abdominal cramps: 42% Diarrhea: 19%	Floppiness, weakness: 93% Poor feeding: 92% Weak suck: 92% Poor feeding: 92% Constipation: 83% Lethargy: 71% Dropping eyelids: 75% Weak cry: 65% Respiratory difficulty: 43%
Signs	Alert mental status: 90% Upper extremity weakness: 75% Ptosis: 73% Lower extremity weakness: 69% Gaze paralysis: 65% Facial palsy: 63% Impaired gag reflex: 58% Tongue weakness: 58% Dilated or fixed pupils: 44% Hyporeflexia or areflexia: 40% Nystagmus: 22% Ataxia: 17%	Poor head control: 97% Difficulty swallowing: 90% Decreased gag reflex: 89% Ptosis: 84% Decreased spontaneous movement: 82% Decreased phonation: 80% Facial weakness: 75% Ophthalmoplegia: 55% Sluggish pupils: 55% Hyporeflexia: 54%

Modified from Long SS. Clostridium botulinum *(botulism). In: Long SS, Pickering LK, Prober CG, eds.* Principles and Practice of Pediatric Infectious Diseases. Philadelphia, *PA: Saunders, Elsevier; 2012:971–979, Copyright Elsevier, 2012, and Overturf GD. Clostridial intoxication and infection. Botulism. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, eds.* Feigin and Cherry's Textbook of Pediatric Infectious Diseases. *7th ed. Philadelphia, PA: Saunders, Elsevier; 2014:1791–1794, Copyright Elsevier, 2014.*

DIFFERENTIAL DIAGNOSIS

The absence of bulbar paralysis should exclude the diagnosis of any form of botulism. Clustering of cases of the neurologic syndrome suggests the possibility of a botulism outbreak. In foodborne botulism, the differential diagnosis can be extensive. Some disorders to consider include myasthenia gravis, Guillain-Barré syndrome (GBS), cerebrovascular accident, Eaton-Lambert syndrome, paralytic shellfish poisoning, chemical intoxication, tick paralysis, and psychiatric disease. (6)

An edrophonium (Tensilon) test should be performed to exclude myasthenia gravis, which usually spares pupillary and oculomotor function. GBS, particularly Fisher-Miller variant (~5% of GBS cases), has an atypical presentation that can mimic botulism but usually shows ascending peripheral paralysis followed by cranial nerve involvement. An elevated protein content in cerebrospinal fluid (CSF) in the absence of cells helps to distinguish GBS from botulism. GBS also has typical electromyography (EMG) findings that distinguish it from botulism. Atypical cases of botulism with asymmetric ptosis or extremity weakness can be more challenging to identify. Some atypical botulism cases might show a positive response to edrophonium, which can further complicate the diagnosis. (6)

Although initial presentation might include gastrointestinal symptoms, the presence of cranial nerve involvement aids in rapid exclusion of ordinary bacterial food poisoning. Shellfish and fish poisonings have a rapid onset and often cause paresthesias and tremors. Mushroom poisoning

results in severe abdominal pain, vomiting, and diarrhea, possibly leading to coma. (6) Atropine poisoning has a very rapid onset accompanied by facial flushing and hallucinations.

In infant botulism, the most common admitting diagnosis is sepsis. Once the hypotonia progresses, other conditions are commonly considered, including hypothyroidism, other neurologic disease, inborn errors of metabolism, poliomyelitis, encephalitis, and poisoning. In infants, the edrophonium (Tensilon) test is typically not indicated because congenital myasthenia gravis can be excluded by the history and de novo myasthenia does not occur in this age group. GBS is rare in infancy and Miller-Fisher variant cases (which can present with cranial nerve palsies similar to botulism) can be distinguished from botulism by CSF analysis, nerve conduction studies, and EMG. Furthermore, GBS occurs in older children compared with 95% of laboratory-confirmed botulism cases occurring in patients younger than age 6 months. (3) A review of 681 infants between 1992 and 2005 in whom infant botulism was suspected identified 32 patients (4.7%) who received either human derived botulinum antitoxin (BIG-IV) or placebo based on clinical suspicion of botulism but eventually alternative diagnoses were identified. (35) The diagnoses that mimicked botulism fell into 5 categories: spinal muscular atrophy (SMA) type I (n=5), metabolic disorders (n=8), infectious diseases (n=3), miscellaneous (n=7), and probable infant botulism (n=9). The diagnosis of infant botulism could not be confirmed on the 9 (28%) patients because of failure to obtain or correctly submit a stool or enema specimen for testing. However, EMG in 5 of the 9 patients showed the characteristic botulism pattern.

Distinctive features of patients with SMA type I are a longer history of generalized weakness that spares extraocular muscles and sphincters, which are characteristically involved in infant botulism. Metabolic disorders necessitate appropriate laboratory studies for diagnosis. (35) Paraneoplastic syndromes with neuromuscular junction involvement have also been described as mimicking infant botulism. (35)

Polio and other nonpolio enterovirus causes of AFP can be distinguished from botulism by the presentation of asymmetric paralysis that is commonly associated with fever, meningismus, CSF pleocytosis, and EMG findings. AFP has a number of infectious and noninfectious causes. Viral pathogens include enterovirus, adenovirus, and West Nile virus. A study investigating AFP in California between 1992 and 1998 found an incidence of 1.4 cases per 100,000 per year in children younger than age 15 years. (36) Among the 245 cases reported, the most common diagnoses were GBS (23%), unspecified AFP (21%), and botulism (12%). Polio and other causes of AFP are very uncommon in the United States. The last case of wild type indigenous polio in North America was reported in 1979 and the last imported case in 1993. Vaccine-associated AFP can occur with the live oral polio virus vaccine, which has not been used in the United States since 2000.

DIAGNOSIS

A good clinical history that includes timing and progression of neurologic symptoms, recent diet, and bowel habits coupled with a high index of suspicion are important to establish the botulism diagnosis. A thorough physical examination may reveal the typical manifestations of progressive symmetric AFP. The initial presentation is bulbar involvement.

Results of most initial laboratory studies are normal except for mild dehydration, which is more common in infants and is related to poor feeding.

The diagnosis is confirmed by detection of the organism or botulinum toxin in patient stools, serum, wound exudates, tissue specimens, or the implicated food source. *C botulinum* is not part of the normal flora of infants or adults, so its presence in culture in a symptomatic individual should be considered diagnostic of botulism. Toxin is detected from specimens using a mouse neutralization assay, which remains the most sensitive and specific method available. (3) Cultures from food, wound, and stools require enriched selective media to isolate *C botulinum*. Laboratory confirmation is essential for appropriate surveillance and reporting and has implications for prognosis because the severity and duration of illness have been reported to be worse in cases due to type A compared with type B toxin. (6)(37)

Botulinum toxin is detected in serum or stool specimens in approximately 46% of clinically diagnosed cases. (3) In foodborne cases, serum toxin assay may remain positive for up to 16 days after admission. Stool cultures grow *C botulinum* in approximately 70% of the cases. (3) Although the organism is more often detectable only in the early stages of disease, it can persist in the stools as long as 5 months in patients with infant botulism.

For infant botulism, toxin can be detected in a serum specimen but only early in the course of the illness and before antitoxin administration. Only about 1% of the cases reported in the United States have a positive serum toxin assay.

Stool, enema, and gastric aspirates are the preferred specimens for culture and toxin assay. Given the difficulty of obtaining stool specimens due to constipation, a sterile, nonbacteriostatic water (not saline) enema specimen should be collected. To increase the likelihood of diagnosis, suspect foods should be collected following CDC protocols. (13)

Specimens that can be submitted to the CDC for botulinum toxin detection include serum, gastric contents or emesis,

feces (at least 20 to 50 g, when possible), and exudates from wounds and tissues. (3) All specimens, but particularly blood, should be obtained as soon as possible after the diagnosis is suspected and before antitoxin administration. Also, the local state health department should be immediately notified. Information regarding appropriate specimen collection and transportation protocols is available through the CDC. (13)

EMG shows a distinctive pattern of brief, small-amplitude, overly abundant motor unit potentials. (38) This test might be extremely useful in differentiating botulism from atypical cases of GBS in adults and other ambiguous cases. The utility of EMG in infant botulism cases is limited because the absence of the characteristic EMG pattern does not exclude the diagnosis, GBS is an extremely rare diagnosis in infants, and the EMG procedure can be painful. (8)(39)

MANAGEMENT

Supportive Care

Botulism neurotoxin binds irreversibly, so administration of antitoxin does not reverse paralysis. Also, neurologic recovery does not occur until the motor neurons regenerate, which can take weeks to months. Accordingly, intensive care, particularly respiratory and nutritional support, is essential.

Antitoxin for Noninfant Forms of Botulism

A heptavalent antitoxin type A to G of equine origin is used in the management of foodborne botulism in adults. It is currently the only antitoxin available in the United States for treatment of noninfant botulism. (40) Antitoxin neutralizes circulating neurotoxin molecules that have not yet bound to nerve endings. The currently recommended dose for adults is one vial per patient as a single dose. (20) It should be procured immediately through the local state health department. The CDC Emergency Operations Center should be contacted at 770-488-7100 for botulism case consultation and antitoxin provision by the health department or if contact with the local health department cannot be established. Additional information may be found at www.bt.cdc.gov/agent/botulism. (16)(19)

Hypersensitivity reactions to the antitoxin occur in about 9% of persons treated with equine sera, so skin testing should be performed before administration. (6)

Antitoxin for Infant Botulism

BIG-IV (or BabyBIG) is licensed by the U.S. Food and Drug Administration for treatment of infant botulism caused by *C botulinum* type A or type B. BIG-IV should be administered urgently and can be obtained through the California Department of Public Health (24-hour telephone number: 510-231-7600; www.infantbotulism.org/). A 5-year, double-blind, placebo-controlled treatment trial in California demonstrated that administration of BIG-IV was safe and effective. It reduced mean hospital stay per case from approximately 5.5 weeks to approximately 2.5 weeks ($P < .001$) and reduced mean hospitalization cost per case by about $100,500 in 2011 dollars ($P < .001$). (37) In a 6-year follow-up open-label study, BIG-IV reduced mean hospital stay to 2.2 weeks when given within 7 days of admission. (3) BIG-IV has been shown to decrease days of mechanical ventilation, days of intensive care unit stay, and overall hospital stays. (3)

Treatment with BIG-IV should be started as early in the illness as possible on the basis of clinical suspicion to provide maximal neutralization of the toxemia. Awaiting confirmatory test results unnecessarily delays treatment.

Antimicrobial Agents

Antibiotics are not indicated for infant botulism. Antibiotics should be reserved for the treatment of secondary bacterial infections (eg, pneumonia, urinary tract infections). If indicated, antibiotics should be administered after prompt use of BIG-IV to neutralize the circulating toxin because antibiotic administration may result in *C botulinum* lysis and subsequent neurotoxin release into the gut lumen. (8)

Aminoglycosides are weak pharmacologic neuromuscular blocking agents and should be avoided because they might potentiate the toxin paralytic effects, precipitating acute respiratory arrest in unsuspected infant botulism patients who are initially being treated for sepsis. (3)(8)

In wound botulism, exploration and wound debridement are indicated, ideally after antitoxin administration. Appropriate anaerobic cultures should be obtained in the operating room. Penicillin is the drug of choice at doses of 250,000 to 400,000 U/kg per day for 10 to 14 days. Metronidazole has been suggested as an alternative, but its effectiveness in botulism has not been demonstrated. (6)

The role of antimicrobial therapy in foodborne or the adult intestinal colonization form of botulism is not established. (6)

PROGNOSIS

As noted previously, botulinum toxin binds irreversibly to the neuromuscular junction synapses, so neurologic recovery does not occur until new motor endplates are regenerated, which can take weeks to months. (38) Convalescence may be prolonged, and some symptoms may persist for as long as 1 year. Complete neurologic recovery is expected in patients with infant botulism. (3)

The nadir of the paralysis in untreated patients who have infant botulism is reached within 1 to 2 weeks after admission,

and signs of recovery only develop 1 to 3 weeks later. Patients treated with BIG-IV have significantly shorter hospital stays, with a mean of 2 weeks. Most infants show gradual improvement over 10 days to 2 months. Common complications include respiratory failure (requiring mechanical ventilation) and secondary infections such as pneumonia, urinary tract infection, and *C difficile*-associated colitis.

The favorable prognosis of botulism in the Unites States is primarily due to progress in intensive supportive care, with a steady decrease in mortality from 60% in the 1950s to 3% to 5% overall today and less than 1% in those who are hospitalized. The fatality rate, however, remains high in resource-poor settings in other areas of the world. Higher morbidity and mortality rates are associated with larger doses of ingested toxin and a shorter incubation period. Mortality is higher in type A than type B or C toxin disease. (6) Early identification of the index case in an outbreak would likely improve the prognosis of others exposed to the same food. Individuals younger than age 20 years often have better outcomes. (6)

Reinfection with the same or a different toxin type of *C botulinum* has not been reported.

PREVENTION AND CONTROL MEASURES

Meticulous handwashing is essential. Isolation measures or "enteric precautions" are not required in foodborne cases because patients ingest the preformed toxin and there is no person-to-person transmission.

In infant botulism cases, however, soiled diapers should be autoclaved because they can contain botulinum neurotoxin and spores. The latter can potentially contaminate open skin lesions of the staff, resulting in wound botulism cases. For this reason, caregivers with hand wounds should avoid handling the diapers. (3)

Botulism is a nationally notifiable disease, and law requires that any suspected case be immediately reported (ie, by phone or fax) to the local state health department. Immediate notification is important to obtain diagnostic aid, determine appropriate collection and handling of specimens, and obtain prompt antitoxin delivery. Immediate notification also is important because of the potential for toxin to be used as a bioterrorism weapon.

Prophylactic equine antitoxin is not recommended for asymptomatic people who have ingested a food known to contain botulinum toxin. People exposed to toxin who are asymptomatic should receive close medical observation. (8)

Due to the association of honey consumption with infant botulism cases, honey should not be given to children younger than age 12 months.

Education about safe practices in food preparation and home canning methods should be promoted. Resources are available through the CDC website. To kill *C botulinum* spores, a pressure cooker must be set at 116°C. Toxin destruction requires cooking of foods until their internal temperature is 85°C for 10 minutes. Bulging food containers should be discarded because they might contain gas produced by *C botulinum*. Foods that appear spoiled should not be tasted or eaten. Additional information is available through the CDC website. (19)

Summary

- On the basis of strong evidence, botulism is a rare, severe, and potentially lethal illness that is caused by the botulinum toxin, which is produced by *Clostridium botulinum* and other clostridial species.
- On the basis of strong evidence, all forms of botulism (foodborne, infant, wound, iatrogenic, and inhalational) produce the same neurologic syndrome characterized by symmetric cranial nerve palsy, commonly followed by afebrile, symmetric descending flaccid paralysis of involuntary muscles, which may result in respiratory compromise and death.
- The mainstays of treatment are early diagnosis, intensive supportive care, and timely botulinum antitoxin administration. Strong research evidence supports the urgent administration of human-derived botulinum antitoxin in suspected infant botulism cases, which has been shown to decrease the length of hospitalization, intensive care unit admission, and mechanical ventilation. (3)(37) Some research and expert consensus advocate the use of heptavalent antitoxin type A to G in noninfant botulism cases. (40)
- Botulism is a mandatory nationally notifiable disease. Clinicians should contact their local health departments as soon as a botulism case is suspected. State public health officials can reach the Centers for Disease Control and Prevention clinical emergency botulism service for consultation and antitoxin 24/7 at 770-488-7100. (16)(19)
- On the basis of consensus, prevention strategies include education about safe food preparation and home canning techniques, (8)(41) keeping wounds clean, and monitoring for signs of infection.
- On the basis of multiple case-control studies that identified the association of honey consumption with infant botulism cases and with consensus of all major pediatric organizations and honey manufacturers, honey should not be fed to children younger than age 12 months. (3)(8)(30)
- The use of aminoglycosides in infants with suspected sepsis or possible botulism should be avoided because aminoglycoside administration might exacerbate paralysis.

CME quiz and References for this article are at http://pedsinreview.aappublications.org/content/37/5/183.

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A 2-year-old girl is admitted to the pediatric ward with suspicion for botulism poisoning. Which of the following findings is most likely to be seen in severe disease?
    A. Alert to time, place, and person.
    B. Ascending paralysis of involuntary muscles.
    C. Fever.
    D. Intact respiratory drive.
    E. Normal deep tendon reflexes.
2. You are preparing a lecture for the microbiology course for second-year medical students. You would like them to understand the neurotoxicity caused by *Clostridium botulinum*. The neurologic complications of human *C botulinum* infection are most commonly due to:
    A. Blocking acetylcholine transmission at the neuromuscular junction because the toxin does not cross the blood-brain barrier.
    B. Neurotoxin F and infrequently neurotoxins A and B.
    C. Paralysis resulting from dopamine accumulation in the presynaptic terminal.
    D. The small lipophilic nature of the *C botulism* toxin that allows easy entry into the central nervous system via the permeable blood-brain barrier.
    E. Upper motor neurons being most affected by the *C botulinum* toxin.
3. You are a general pediatrician in northern California where there is a high incidence of infant botulism. During health supervision visits, you counsel caregivers of infants younger than age 12 months on the behaviors that put infants at higher risk for acquiring the infection. Which of the following statements would you include in your counseling to provide the most accurate information regarding infant botulism?
    A. According to the Centers for Disease Control and Prevention, infant botulism has a high likelihood of person-to-person transmission.
    B. Because of public awareness campaigns, infant botulism attributed to consumption of contaminated honey no longer occurs.
    C. Infant botulism is most common on the continent of Africa, likely due to poor living conditions and contaminated water supplies.
    D. Infant botulism is the second most common form of botulism reported in the United States, with foodborne botulism as most common.
    E. Symptomatic disease in infants is due to the transmission of *C botulinum* spores into the intestinal tract of infants followed by spore germination and toxin production.
4. A 17-year-old girl has been diagnosed with foodborne botulism. She had developed respiratory compromise upon presentation to a pediatric emergency department this evening. Her medical team is attributing her infection to undercooked poultry she ate 6 to 7 hours ago while dining with her family for lunch at a new restaurant in town. She developed abdominal distension, vomiting, diarrhea, and hematemesis followed by difficulty speaking and swallowing. Which of the following details from the patient presentation is most consistent with *C botulinum* poisoning?
    A. Abdominal distension.
    B. Difficulty speaking and swallowing.
    C. Hematemesis.
    D. Transmission through consumption of undercooked poultry.
    E. Vomiting and diarrhea.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

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This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

5. A 9-month-old boy presents to the clinic with a 2-day history of vomiting and lethargy. He is admitted to the hospital ward for a sepsis evaluation and started on antibiotics. Once admitted, he develops progressive hypotonia, evidenced by weak cry and poor head control. Which of the following symptoms distinguishes infant botulism from other food poisoning caused by bacteria?

   A. Cranial nerve involvement.
   B. Dehydration.
   C. Peripheral nervous system involvement.
   D. Rapid onset.
   E. Severe abdominal pain.

Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/health-issues/conditions/infections/Pages/Botulism.aspx
- Spanish: https://www.healthychildren.org/spanish/health-issues/conditions/infections/paginas/botulism.aspx

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DOI: 10.1542/pir.2015-0018

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