# Botulism in the United States: A Clinical and Epidemiologic Review

Roger L. Shapiro, MD; Charles Hatheway, PhD†; and David L. Swerdlow, MD

Botulism is caused by a neurotoxin produced from the anaerobic, spore-forming bacterium *Clostridium botulinum*. Botulism in humans is usually caused by toxin types A, B, and E. Since 1973, a median of 24 cases of foodborne botulism, 3 cases of wound botulism, and 71 cases of infant botulism have been reported annually to the Centers for Disease Control and Prevention (CDC). New vehicles for transmission have emerged in recent decades, and wound botulism associated with black tar heroin has increased dramatically since 1994. Recently, the potential terrorist use of botulinum toxin has become an important concern.

Botulism is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Blurred vision, dysphagia, and dysarthria are common initial complaints. The diagnosis of botulism is based on compatible clinical findings; history of exposure to suspect foods; and supportive ancillary testing to rule out other causes of neurologic dysfunction that mimic botulism, such as stroke, the Guillain–Barré syndrome, and myasthenia gravis. Laboratory confirmation of suspected cases is performed at the CDC and some state laboratories. Treatment includes supportive care and trivalent equine antitoxin, which reduces mortality if administered early. The CDC releases botulism antitoxin through an emergency distribution system. Although rare, botulism outbreaks are a public health emergency that require rapid recognition to prevent additional cases and to effectively treat patients. Because clinicians are the first to treat patients in any type of botulism outbreak, they must know how to recognize, diagnose, and treat this rare but potentially lethal disease.

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From the Centers for Disease Control and Prevention, Atlanta, Georgia. For current author addresses, see end of text.

†Deceased

Botulism is a neuroparalytic illness caused by a neurotoxin produced from the anaerobic, spore-forming bacterium *Clostridium botulinum* (1). Botulism was recognized as "sausage poisoning" during the 18th and 19th centuries (2), and the pathogenesis of disease was first described by van Ermengem in 1897 after his investigation of a large outbreak in Ellezelles, Belgium (3). Because botulinum toxin is so lethal, intensive surveillance and control measures have been mandated in the United States. However, prompt recognition and treatment of botulism by clinicians remain a critical component of surveillance and are the most important steps in reducing rates of death from this disease. Botulism outbreaks are a public health emergency that require rapid recognition to prevent additional cases and to effectively treat patients with mechanical ventilation and early administration of antitoxin. In the event of terrorist use of botulinum toxin, clinicians would also be the first to recognize and treat casualties of intentional botulism poisoning. In this report, we provide a clinical overview of botulism and describe the U.S. Botulism Surveillance System.

## The Organism

*Clostridium botulinum* is classified as a single species but consists of at least three genetically distinguishable groups of organisms. These are alike in their abilities to produce neurotoxins with similar pharmacologic activities (4) but diverse serologic properties (toxin types A, B, C, D, E, F, and G). Human botulism is primarily caused by the strains of *C. botulinum* that produce toxin types A, B, and E. Neurotoxigenic strains of *C. baratii* (5, 6) (which produce type F toxin) and *C. butyricum* (7) (which produce type E toxin) also have been implicated in human botulism. Strains of *C. botulinum* that produce type C or type D toxin for the most part cause botulism only in nonhuman species.

These neurotoxigenic organisms are anaerobic, gram-positive, spore-forming bacilli and are commonly found in soils throughout the world. *Clostridium botulinum* organisms cause food poisoning because the heat-resistant spores survive food preservation

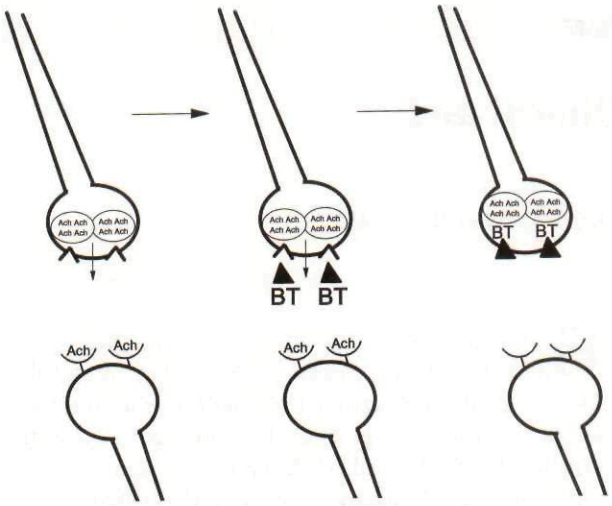


**Figure 1. Schematic representation of the action of botulinum toxin (*BT*) on a neuromuscular junction.** Ach = acetylcholine.

methods that kill nonsporulating organisms; they subsequently produce a potent neurotoxin under anaerobic, low-acid (pH > 4.6), and low solute conditions (8). The toxins affect a broad range of vertebrate species, but the evolutionary utility of toxin production to the bacterial host organisms is unclear.

## The Toxin

The seven recognized types of botulinum neurotoxins (types A through G) are distinguished by neutralization of biological activity with type-specific serologic reagents. These types are defined by the International Standards for *Clostridium botulinum* Antitoxin (9). The toxins of all types consist of a 100-kd heavy chain joined to a 50-kd light chain by a disulfide bond (10). After absorption into the bloodstream, botulinum toxin binds irreversibly to the presynaptic nerve endings of the peripheral nervous system and cranial nerves, where it inhibits the release of acetylcholine (**Figure 1**). The mechanism involves binding to a toxin receptor on the nerve cell membrane at the neuromuscular junction, internalization of a portion (the catalytic portion residing in the light chain) of the toxin molecule (11), and cleavage of protein components of the neuroexocytosis apparatus within the cell (12).

Botulinum neurotoxin is considered the most potent lethal substance known. It is 15 000 to 100 000 times more toxic than sarin, the potent organophosphate nerve agent used in a terrorist attack in the subway system in Tokyo (13). The nucleotide sequences for all seven toxin types have been sequenced (14–22).

## Epidemiology

Four clinical forms of botulism occur in humans: foodborne botulism; wound botulism; infant botulism (infant intestinal colonization); and, rarely, adult infectious botulism (adult intestinal colonization). Studies in monkeys indicate that, if aerosolized, botulinum toxin also can be absorbed through the lungs (23); this could occur in the case of a terrorist attack. From 1973 through 1996 in the United States, 724 cases of foodborne botulism (median, 24 cases annually [range, 8 to 86 cases]), 103 cases of wound botulism (median, 3 cases annually [range, 0 to 25 cases]), 1444 cases of infant botulism (median, 71 cases annually [range, 0 to 99 cases]), and 39 cases of botulism of undetermined type were reported to the Centers for Disease Control and Prevention (CDC) (**Figure 2**) (CDC. Unpublished data). In the United States, approximately half of the cases of foodborne botulism are caused by toxin type A; the remaining foodborne cases are almost equally divided between toxins type E and type B (24). Among cases of infant botulism, approximately half are caused by toxin type A and half by toxin type B; among cases of wound botulism, approximately 80% are caused by toxin type A and 20% by toxin type B (CDC. Unpublished data). In the United States, type A botulism is most common west of the Mississippi River, and type B is most common east of the Mississippi River (25). Type E outbreaks are most common in Alaska (26, 27).

Important changes in the epidemiology of botulism have emerged in the past few decades. Recently identified vehicles for foodborne botulism include homemade salsa (24), baked potatoes sealed in aluminum foil (28), cheese sauce (29), sautéed onions held under a layer of butter (30), garlic in oil (31), and traditionally prepared salted or fermented

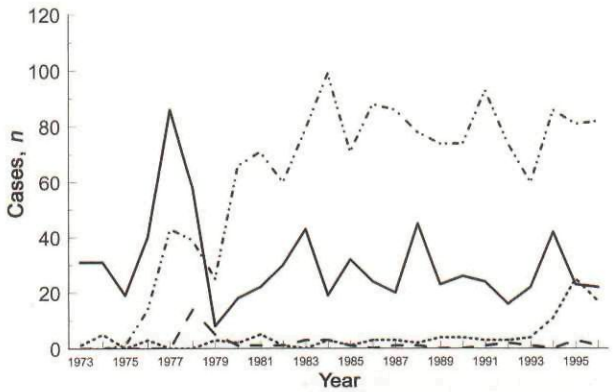


**Figure 2. Annual incidence of botulism in the United States, 1973 to 1996.** The line interspersed with dots indicates botulism in infants, the solid line indicates foodborne botulism, the short-dashed line indicates wound botulism, and the long-dashed line indicates botulism from an undetermined source.

**Table 1. Vehicles Associated with Foodborne Botulism**

| |
|---|
| Home-canned or home-processed low-acid (pH > 4.6) foods |
| Vegetables |
| Meats |
| Fish |
| Fermented or salted fish products |
| Whale or seal products |
| Relish |
| Chili peppers |
| Salsa |
| Baked potatoes in aluminum foil |
| Garlic in oil |
| Sautéed onions kept under butter sauce |
| Cheese sauce |

fish (26) (**Table 1**). From 1976 through 1984, restaurant-associated outbreaks accounted for a large proportion of botulism cases (42%), although only 4% of all outbreaks were restaurant-associated (32). The largest of these outbreaks were caused by jalapeño peppers in Michigan in 1977, potato salad in New Mexico in 1978, sautéed onions in Illinois in 1983, and skordalia made with baked potatoes in Texas in 1994 (33).

In 1995 and 1996, the occurrence of wound botulism increased (34), with a total of 42 cases (CDC. Unpublished data). Most of these cases occurred among heroin users in California who injected the drug subcutaneously. Although it is unclear what factors contributed to this epidemic, a shift to the use of black tar heroin produced in Mexico may have played a role (35).

Purified botulinum toxin is used to treat various medical conditions, such as strabismus, blepharospasm, torticollis, oromandibular dystonia, spasmodic dysphonia, and achalasia. Systemic symptoms of botulism-like illness have been reported after therapeutic administration of botulinum toxin (36) but are unlikely to have resulted from this procedure. It is estimated that for most patients, at least 10 times the treatment dose would be required to enter the circulation for systemic symptoms to result (37; CDC. Unpublished data).

The potential for intentional poisoning with botulinum toxin has come into clearer focus in recent years. As many as 17 countries are suspected to include or to be developing biological agents in their offensive weapons programs (38). Botulinum toxin often is one of these agents because it is relatively easy to produce and is highly lethal in small quantities. In August 1995, Iraq revealed that during the Persian Gulf War, 11 200 L of botulinum toxin preparation was loaded into specially designed SCUD missile warheads (39). In addition, before the Aum Shinrikyo used sarin in the 1995 terrorist attack on the Tokyo subway system, the cult had produced botulinum toxin (40).

## Clinical Features

### Foodborne Botulism

Foodborne botulism is caused by ingestion of preformed toxin produced in food by *C. botulinum*. The most frequent source is home-canned foods, in which spores that survive an inadequate cooking and canning process germinate, reproduce, and produce toxin in the anaerobic environment of the canned food. In the event of intentional foodborne poisoning with botulinum toxin, the signs and symptoms developing after ingestion would probably resemble those of naturally occurring foodborne botulism. If aerosolized toxin was inhaled, the incubation period might be slightly longer (23), and gastrointestinal symptoms might not occur.

The clinical syndrome of foodborne botulism is dominated by neurologic symptoms and signs resulting from a toxin-induced blockade of the voluntary motor and autonomic cholinergic junctions (**Table 2**). Although the syndrome is similar for each toxin type, type A toxin has been associated with more severe disease and a higher fatality rate than type B or type E toxin (41). Symptoms from any toxin type may range from subtle motor weakness or cranial nerve palsies to rapid respiratory arrest. The initial symptoms of foodborne botulism may be gastrointestinal and can include nausea, vomiting, abdominal cramps, or diarrhea; after the onset of neuro-

**Table 2. Commonly Reported Clinical Symptoms and Physical Findings in Botulism***

| |
|---|
| Symptoms |
| Gastrointestinal |
| Nausea |
| Diarrhea (early) |
| Constipation (late) |
| Abdominal cramps |
| Vomiting |
| Neurologic |
| Blurred vision |
| Dysphagia |
| Dry mouth |
| Diplopia |
| Dysarthria |
| Arm weakness |
| Leg weakness |
| Dyspnea |
| Miscellaneous |
| Fatigue |
| Sore throat |
| Dizziness |
| Physical findings |
| Ptosis |
| Extraocular muscle weakness |
| Facial nerve dysfunction |
| Hypoactive gag reflex |
| Tongue weakness |
| Pupils fixed or dilated |
| Extremity weakness |
| Symmetric |
| Proximal to distal |
| Descending pattern |
| Nystagmus |
| Hypoactive deep-tendon reflexes |

* Adapted from Hughes et al. (42).

logic symptoms, constipation is more typical. Dry mouth, blurred vision, and diplopia are usually the earliest neurologic symptoms. These initial symptoms may be followed by dysphonia, dysarthria, dysphagia, and peripheral muscle weakness. Symmetric descending paralysis is characteristic of botulism; paralysis begins with the cranial nerves, then affects the upper extremities, the respiratory muscles, and, finally, the lower extremities in a proximal-to-distal pattern. Onset usually occurs 18 to 36 hours after exposure (range, 6 hours to 8 days) (42). In severe cases, extensive respiratory muscle paralysis leads to ventilatory failure and death unless supportive care is provided. Patients have required ventilatory support for up to 7 months before the return of muscular function, but ventilatory support is most commonly needed for 2 to 8 weeks (43).

Clinical recovery generally occurs over weeks to months; electron microscopic evidence suggests that clinical recovery correlates with the formation of new presynaptic end plates and neuromuscular junctions (44, 45). Before mechanical ventilation and intensive supportive care, up to 60% of patients died; since the 1950s, however, the mortality rate from botulism has steadily decreased (43). Death now occurs in 5% to 10% of cases of foodborne botulism; early deaths result from a failure to recognize the severity of disease, whereas deaths after 2 weeks result from complications of long-term mechanical ventilatory management (42).

### Wound Botulism

Wound botulism occurs when anaerobic conditions within an abscessed wound allow germination of *C. botulinum* spores, subsequent multiplication of the organism, and production and absorption of toxin in vivo. The clinical manifestations are similar to those seen in foodborne botulism, except that gastrointestinal symptoms are absent and the median incubation period is longer (7 days [range, 4 to 14 days]) (46). The case-fatality rate for wound botulism is approximately 15% (47).

### Infant Botulism

Botulism in infants due to intestinal colonization represents a distinct clinical entity in which *C. botulinum* spores enter and colonize the gastrointestinal tract and produce toxin. The disease most commonly occurs during the second month of life. Constipation is usually the earliest clinical sign, followed by poor feeding; lethargy; a weak cry; decreased sucking; and generalized lack of muscle tone, noticeably characterized by a floppy head (48). The spectrum of disease is wide, ranging from mild constipation to sudden death, although recovery generally occurs over weeks to months (49). The source of ingestion is unknown in approximately 85% of cases; in up to 15% of cases, the ingestion of honey is suspected (49, 50). The risk factors for infant botulism are poorly described; for unclear reasons, the disease does not occur in outbreaks, and it is thought that host susceptibility factors may play an important role (50).

### Adult Infectious Botulism

In rare instances, botulism in adults also can occur as a result of intestinal colonization with *C. botulinum* and in vivo toxin production in a manner similar to that of infant botulism (51, 52). Such patients often have a history of abdominal surgery, gastrointestinal tract abnormalities, or recent antibiotic treatment that may disrupt the natural gastrointestinal flora (53, 54). Cases have been caused by toxin types A and B; in addition, three cases involving type F toxin produced by *C. baratii* were confirmed by the CDC (6, 24).

## Diagnosis

### Clinical Findings

Botulism is underdiagnosed because many clinicians are unfamiliar with the disease and because symptoms can be mistaken for more common clinical entities, such as stroke or the Guillain–Barré syndrome (52, 55). However, the diagnosis of botulism is not difficult in most cases once it has been considered. Botulism should be suspected in a patient with acute onset of gastrointestinal, autonomic (such as dry mouth or difficulty focusing eyes), and cranial-nerve (diplopia, dysarthria, dysphagia) dysfunction. The diagnosis is even more likely if the patient has recently eaten home-canned foods or if family members or companions who have shared meals are similarly ill.

### Ancillary Testing

Because of the importance of early treatment, botulism must be diagnosed initially on the basis of the history and physical findings before toxin testing and culturing can be performed. The differential diagnosis for botulism includes the Guillain–Barré syndrome (especially the Miller–Fisher variant), myasthenia gravis, the Eaton–Lambert syndrome, and the stroke syndrome; intoxication with organophosphates, atropine, carbon monoxide, or aminoglycosides; and tick paralysis, paralytic shellfish poisoning, and puffer fish ingestion (55). The diagnosis of botulism is supported by ancillary testing (**Table 3**), such as documentation of a normal result on magnetic resonance imaging or computed tomography of the brain to rule out stroke syndrome; a normal result on lumbar puncture to differentiate botulism

from the Guillain–Barré syndrome, which typically causes elevated levels of protein in the cerebrospinal fluid (although protein levels may be normal initially); and a negative edrophonium chloride test result to rule out myasthenia gravis (although transient responses may occasionally be noted in botulism). Electromyography usually reveals decreased amplitude of action potentials in affected muscle groups, but this finding is relatively nonspecific. An incremental increase in amplitude to rapid repetitive electromyography by using frequencies of 20 to 50 Hz is more helpful and may distinguish botulism from the Guillain–Barré syndrome or myasthenia gravis but not the Eaton–Lambert syndrome. Electromyography should be performed by a person experienced in performing rapid repetitive testing (55).

In most cases, lumbar puncture and brain imaging can be performed within hours of presentation. Negative results may raise the clinical suspicion for botulism and should prompt close monitoring for respiratory compromise; rapid repetitive electromyography; and, possibly, edrophonium chloride testing. State or local health officials should be contacted to discuss potential measures for preventing additional cases; the possible release of antitoxin by CDC; and the collection of serum and stool samples at the earliest possible opportunity to confirm the diagnosis of botulism by the detection of toxin if none of the ancillary tests is pathognomonic.

### Toxin and Microbiological Testing

In cases of suspected foodborne botulism, serum and stool specimens and epidemiologically implicated foods should be tested for botulism neurotoxin. The most reliable method for the detection of toxin is the mouse inoculation test; this can be performed at the CDC or some state public health laboratories. Botulinum toxin type is determined by neutralizing the biological activity of toxic samples injected into mice with type-specific botulism antitoxin. Symptoms of botulism and death occur in mice injected with unneutralized samples but not in mice injected with neutralized samples (56). Efforts to replace mouse inoculation testing with in vitro tests for botulism antitoxin, such as enzyme-linked immunosorbent assays (57) or polymerase chain reaction (58), remain experimental.

Toxin is detected in serum or stool specimens in approximately 46% of clinically diagnosed cases. Stool specimens also should be cultured for *C. botulinum* because a positive *C. botulinum* culture from stool is also considered confirmatory for botulism. Isolation of neurotoxigenic organisms from stool specimens increased the sensitivity of laboratory testing to 73% in one case series (59) and 67% in another (41). Detection of botulinum toxin from epidemiologically implicated food may provide additional confirmatory evidence for botulism; however, the isolation of *C. botulinum* organisms from a food devoid of toxin usually has little significance because spores are ubiquitous in the environment. If wound botulism is suspected, such specimens as wound exudate, a tissue sample, or a swab sample should be obtained for anaerobic culture in addition to a serum toxin assay. A stool specimen may be examined to exclude food or intestinal colonization as sources of toxin. Infant botulism should be suspected in any infant with constipation, poor feeding, diminished sucking and crying ability, neck and peripheral muscle weakness, or ventilatory distress. Stool cultures for *C. botulinum* and testing for the presence of toxin in stool should be performed in such patients.

**Table 3. Tests That Are Useful in the Diagnosis of Botulism***

| Test | Result Consistent with Botulism |
|---|---|
| Initial test | |
| Brain imaging (CT or MRI) | Normal |
| Lumbar puncture | Normal |
| Electromyography | Decreased amplitude of action potentials in involved muscle groups |
| Rapid repetitive electromyography (20–50 Hz) | Facilitation (increasing pattern of action potential amplitude) |
| Edrophonium chloride test | Negative |
| Confirmatory test | |
| Mouse inoculation test for toxin (serum, stool, or food) | Positive |
| Stool culture for *Clostridium botulinum* | Positive |

* CT = computed tomography; MRI = magnetic resonance imaging.

## Management

### Individual Patients

#### *Supportive Measures*

The mainstay of treatment for severe botulism is supportive therapy with mechanical ventilation, which has substantially decreased mortality rates in the past 40 years. Because respiratory arrest may be rapid, patients suspected of having botulism should be monitored initially in an intensive care unit, the vital capacity should be checked frequently, and mechanical ventilation should be initiated at the earliest signs of respiratory decompensation. In addition, gastric lavage should be attempted if the potential food exposure was recent; in the absence of profound ileus, cathartic agents or enemas may be useful for removing unabsorbed toxin from the gastrointestinal tract. Cathartic agents containing magnesium should be avoided because of the theoretical concern that increased magnesium levels may enhance the action of botulinum toxin. If wound botulism is suspected, surgical debridement should be

performed and antimicrobial treatment (such as penicillin) should be given.

### *Antitoxin Administration*

The administration of antitoxin is the only specific pharmacologic treatment available for botulism. The currently available licensed antitoxin is an equine product with antibodies to toxin types A, B, and E. The administration of trivalent equine antitoxin to humans by the intravenous route neutralizes toxin molecules that are not yet bound to nerve endings. Before 1996, two to four 10-mL vials were administered to each adult patient suspected of having botulism; however, one vial (7500 IU of type A, 5500 IU of type B, and 8500 IU of type E antitoxins) per patient is now administered, and it is believed that no additional doses are necessary. Each vial contains an amount of antitoxin that is more than 100-fold greater than that needed to neutralize the largest amount of circulating antitoxin ever measured at the CDC (60). The circulating antitoxins have a half-life of 5 to 8 days, and a hypersensitivity reaction has been reported for up to 9% of patients (60, 61). After the change to single-vial dosing, the incidence of hypersensitivity may be smaller than that previously reported.

If it is administered early during the course of neurologic dysfunction, antitoxin is effective in preventing progression of illness and shortening the duration of ventilatory failure in severe cases of botulism (62). A retrospective analysis of 134 cases of type A botulism showed an overall mortality rate of 10% among patients who received early treatment with antitoxin (within 24 hours of symptom onset) compared with 15% among those who received late treatment (more than 24 hours after symptom onset) and 46% among those who did not receive antitoxin. In addition, survivors who received antitoxin early had a median hospital stay of only 10 days compared with 41 days for those who received antitoxin late and 56 days for those who did not receive antitoxin (62). More than 80% of patients with adult infectious botulism in the United States are treated with antitoxin. The remaining 20% generally have such a prolonged delay in diagnosis that treatment is considered to be of no benefit; therefore, antitoxin is not administered. Equine antitoxin therapy has not been recommended for infant botulism because of early observations (since disproved) that serum toxin was not detected in such cases and because of concerns about hypersensitivity reactions to this product (61). The safety and efficacy of a human-derived antitoxin product (human botulism immune globulin) administered to infants with botulism are being determined (49). As of June 1998, this product is available in the United States solely for the treatment of infant botulism, under a Treatment Investigational New Drug protocol. For information on obtaining human botulism immune globulin, contact the California Department of Health Services at 510-540-2646 (24 hours).

### Management of Large Outbreaks

In the event of a large outbreak of botulism caused by an enteric or aerosolized route of exposure, the primary means of treating victims would be supportive care through the rapid mobilization of mechanical ventilators. Emergency support with intubation and manual ventilation would be critical during the early hours. Rapid administration of botulism antitoxin is the only pharmacologic treatment available and would probably reduce mortality rates. In U.S. Army experiments, equine $F(ab')_2$ botulism antitoxin given therapeutically to rhesus monkeys as late as 24 hours after an aerosol challenge with a lethal dose of type A toxin resulted in high rates of survival. Without mechanical ventilation, however, the toxin was uniformly lethal if antitoxin administration was delayed until clinical signs had occurred (29 to 46 hours after exposure) (12). Prophylactic immunization with a vaccine against botulinum toxin would also protect against an exposure to botulinum toxin. However, the botulism toxoid vaccine is unlicensed, and the vaccination process must be started months before exposure. The vaccine does not provide life-long immunity, and administration is impractical except for a select high-risk group (such as laboratory workers who work with botulism specimens or military personnel with risk for exposure in battlefield conditions). In most instances, if exposure to a food contaminated by botulinum toxin is suspected in an outbreak setting, asymptomatic persons should be monitored closely without specific therapy and treatment with antitoxin should be initiated at the earliest signs of illness.

## Surveillance and Public Health Response

Because cases of foodborne botulism result from ingestion of contaminated food that may still be available to cause illness in others, a single case of foodborne botulism represents a public health emergency and may herald the beginning of a larger outbreak. Investigation of a suspected case of botulism includes a search for other possible cases, identification of suspect food exposures, and diagnostic testing of both cases and foods as needed. Rapid assessment to determine the source of contamination can lead to appropriate control measures, such as impounding home-canned foods, closing a restaurant, or instituting an emergency product recall. Efforts to locate persons exposed to the same suspect

food may lead to early diagnosis in persons in whom the diagnosis might otherwise be missed altogether.

The CDC maintains intensive surveillance for cases of botulism in the United States in collaboration with state health departments. To identify possible outbreaks rapidly, the CDC provides epidemiologic consultation and laboratory diagnostic services to state and local health departments for suspected cases of foodborne and wound botulism and supplies antitoxin for probable cases at the request of state health departments. Physicians are encouraged to contact their state epidemiologists as soon as they suspect botulism in a patient. State epidemiology offices maintain emergency contact numbers and can assist in diagnosing, managing, and preventing botulism. Epidemiologists from the Foodborne and Diarrheal Diseases Branch at the CDC are available 24 hours a day to answer calls from state health officials treating potential cases of botulism (telephone 404-639-2206; emergency telephone 404-639-2888). In collaboration with state epidemiology offices, CDC epidemiologists recommend appropriate laboratory testing (performed at the CDC or in state laboratories) and ancillary studies to confirm or rule out the diagnosis. Local public health authorities and national food safety authorities should be involved as soon as foodborne botulism is suspected so that possible sources can be investigated and the need for further investigation and preventive measures can be determined.

When foodborne, wound, or adult infectious botulism is suspected, antitoxin is released from CDC quarantine stations. The rapid investigation of cases by local health officials, state epidemiologists, and the CDC prevents additional cases of botulism from implicated foods. Because infant botulism does not occur in outbreaks, the rapid consultation and response mechanism is not used for cases of infant botulism. If human botulism immune globulin, the human antitoxin product under investigation for treatment of infants, is licensed for distribution (49), it will be made available in a separate formulation for use in infants only. Until licensure, the California Department of Health Services can be contacted for information on human botulism immune globulin.

## Conclusions

Botulism is a rare but potentially fatal illness, and prompt recognition of the clinical syndrome plays an important role in decreasing mortality rates. Physicians trained in internal medicine, emergency medicine, critical care, neurology, and infectious diseases may be needed to coordinate case-management efforts as soon as the diagnosis is suspected and before laboratory confirmation of the toxin. In a foodborne outbreak or an intentional poisoning, clinicians may be the first to recognize an ongoing public health emergency. State and local epidemiologists should be informed of all suspected botulism cases to determine potential vehicles of transmission, prevent additional cases, and obtain samples of implicated foods for testing. Epidemiologists at the CDC are available 24 hours a day for clinical consultation and release of antitoxin when appropriate.

*In memoriam:* Dr. Charles Hatheway passed away after this manuscript was completed. Dr. Hatheway dedicated his life to the study of botulism and contributed significantly to our understanding of this disease. He will be greatly missed.

*Requests for Reprints:* David L. Swerdlow, MD, Centers for Disease Control and Prevention, 1600 Clifton Road, MS A-38, Atlanta, GA 30333.

*Current Author Addresses:* Drs. Shapiro and Swerdlow: Centers for Disease Control and Prevention, 1600 Clifton Road, MS A-38, Atlanta, GA 30333.

## References

1. **Smith LD, Sugiyama H.** Botulism: The Organism, Its Toxins, The Disease. 2d ed. Springfield, IL: Charles C. Thomas; 1988.
2. **Meyer KF.** The rise and fall of botulism. Calif Med. 1973;118:63-4.
3. **van Ermengem E.** Classics in infectious disease. A new anaerobic bacillus and its relation to botulism. E. van Ermengem. Originally published as "Über einen neuen anaeroben Bacillus und seine Beziehungen zum Botulismus," in *Zeitschrift für Hygiene und Infektionskrankheiten*, 26:1-56. 1897. Rev Infect Dis. 1979;1:701-19.
4. **Cato EP, George WL, Finegold SM.** Genus *Clostridium*. In: Sneath PH, Mair NS, Sharpe ME, Hold JG, eds. Bergey's Manual of Systematic Bacteriology. v 2. Baltimore: Williams & Wilkins; 1986:1141.
5. **Hall JD, McCroskey LM, Pincomb BJ, Hatheway CL.** Isolation of an organism resembling *Clostridium baratii* which produces type F botulinal toxin from an infant with botulism. J Clin Microbiol. 1985;21:654-5.
6. **McCroskey LM, Hatheway CL, Woodruff BA, Greenberg JA, Jurgenson P.** Type F botulism due to neurotoxigenic *Clostridium baratii* from an unknown source in an adult. J Clin Microbiol. 1991;29:2618-20.
7. **Aureli P, Fenicia L, Pasolini B, Gianfranceschi M, McCroskey LM, Hatheway CL.** Two cases of type E infant botulism caused by neurotoxigenic *Clostridium butyricum* in Italy. J Infect Dis. 1986;154:207-11.
8. **Lund BM.** Foodborne disease due to *Bacillus* and *Clostridium* species. Lancet. 1990;336:982-6.
9. **Bowmer EJ.** Preparation and assay of the international standards for *Clostridium botulinum* types A, B, C, D and E antitoxins. Bull World Health Organ. 1963;29:701-9.
10. **Hatheway CL.** Toxigenic clostridia. Clin Microbiol Rev. 1990;3:66-98.
11. **Halpern JL, Neale EA.** Neurospecific binding, internalization, and retrograde axonal transport. In: Montecucco C, ed. Clostridial Neurotoxins. Current Topics in Microbiology and Immunology. v 195. New York: Springer; 1995:221.
12. **Schiavo G, Rossetto O, Tonello F, Montecucco C.** Intracellular targets and metalloprotease activity of tetanus and botulism neurotoxins. Curr Top Microbiol Immunol. 1995;195:257-74.
13. **Eitzen LT, Caudle MA.** Medical Management of Biological Casualties. Fort Detrick, MD: U.S. Army Medical Research Institute of Infectious Diseases; 1993. Publication no. 20170-5011.
14. **Thompson DE, Brehm JK, Oultram JD, Swinfield TJ, Shone CC, Atkinson T, et al.** The complete amino acid sequence of the *Clostridium botulinum* type A neurotoxin, deduced by nucleotide sequence analysis of the encoding gene. Eur J Biochem. 1990;189:73-81.
15. **Binz T, Kurazono H, Willie M, Frevert J, Wernars K, Niemann H.** The complete sequence of botulism neurotoxin type A and comparison with other clostridial neurotoxins. J Biol Chem. 1990;265:9153-8.
16. **Whelan SM, Elmore MJ, Bodsworth NJ, Brehm JK, Atkinson T, Minton NP.** Molecular cloning of the *Clostridium botulinum* structural gene encoding the type B neurotoxin and determination of its entire nucleotide sequence. Appl Environ Microbiol. 1992;58:2345-54.
17. **Hauser D, Eklund MW, Kurazono H, Binz T, Niemann H, Gill DM, et al.** Nucleotide sequence of *Clostridium botulinum* $C_1$ neurotoxin. Nucleic Acids Res. 1990;18:4924.
18. **Binz T, Kurazono H, Popoff MR, Eklund MW, Sakaguchi G, Kozaki S, et al.** Nucleotide sequence of the genes encoding *Clostridium botulinum* neurotoxin type D. Nucleic Acids Res. 1990;18:5556.
19. **Whelan SM, Elmore MJ, Bodsworth NJ, Atkinson T, Minton NP.** The complete amino acid sequence of *Clostridium botulinum* type-E neurotoxin,

derived by nucleotide-sequence analysis of the encoding gene. Eur J Biochem. 1992;204:657-67.
20. **Elmore MJ, Hutson RA, Collins MD, Bodsworth NJ, Whelan SM, Minton W.** Nucleotide sequence of the gene encoding for proteolytic (Group 1) *Clostridium botulinum* type F neurotoxin: genealogical comparison with other clostridial neurotoxins. Systematic and Applied Microbiology. 1995;18:23-31.
21. **East AK, Richardson PT, Allaway D, Collins M, Roberts TA, Thompson DE.** Sequence of the gene encoding type F neurotoxin of *Clostridium botulinum*. FEMS Microbiol Lett. 1992;75:225-30.
22. **Campbell K, Collins MD, East AK.** Nucleotide sequence of the gene coding for *Clostridium botulinum* (*Clostridium argentinense*) type G neurotoxin: genealogical comparison with other clostridial neurotoxins. Biochem Biophys Acta. 1993;1216:487-91.
23. **McNally RE, Morrison MB, Berndt JE, Fisher JE, Bo-Berry JI, Packett VE, et al.** Effectiveness of Medical Defense Interventions against Predicted Battlefield Levels of Botulinum Toxin A. Joppa, MD: Science Applications International; 1994.
24. **Hughes JM, Hatheway CL, Ostroff SM.** Botulism. In: Scheld WM, Whitley RJ, Durack DT, eds. Infections of the Central Nervous System. 2d ed. Philadelphia: Lippincott–Raven; 1997:615.
25. **Horwitz MA, Hughes JM, Merson MH, Gangarosa EJ.** Food-borne botulism in the United States, 1970-1975. J Infect Dis. 1977;136:153-9.
26. **Wainwright RB, Heyward WL, Middaugh JP, Hatheway CL, Harpster AP, Bender TR.** Food-borne botulism in Alaska, 1947-1985: epidemiology and clinical findings. J Infect Dis. 1988;157:1158-62.
27. **Eisenberg MS, Bender TR.** Botulism in Alaska, 1947 through 1974. Early detection of cases and investigation of outbreaks as a means of reducing mortality. JAMA. 1976;235:35-8.
28. **Seals JE, Snyder JB, Edell TA, Hatheway CL, Johnson CJ, Swanson RC, et al.** Restaurant-associated type A botulism: transmission by potato salad. Am J Epidemiol. 1981;113:436-44.
29. **Townes JM, Cieslak PR, Hatheway CL, Solomon HM, Holloway JT, Baker MP, et al.** An outbreak of type A botulism associated with a commercial cheese sauce. Ann Intern Med. 1996;125:558-63.
30. **MacDonald KL, Spengler RF, Hatheway CL, Hargrett NT, Cohen ML.** Type A botulism from sautéed onions. Clinical and epidemiologic observations. JAMA. 1985;253:1275-8.
31. **St. Louis ME, Peck SH, Bowering D, Morgan GB, Blatherwick J, Banerjee S, et al.** Botulism from chopped garlic: delayed recognition of a major outbreak. Ann Intern Med. 1988;108:363-8.
32. **MacDonald KL, Cohen ML, Blake PA.** The changing epidemiology of adult botulism in the United States. Am J Epidemiol. 1986;124:794-9.
33. Botulism (foodborne)—by year, United States, 1975-1994. MMWR Morb Mortal Wkly Rep. 1995;43:22.
34. Wound botulism—California, 1995. MMWR Morb Mortal Wkly Rep. 1995; 44:889-92.
35. **Passaro DJ, Werner SB, McGee J, MacKenzie WR, Vugia DJ.** Wound botulism associated with black tar heroin among injecting drug users. JAMA. 1998;279:859-63.
36. **Bakheit AM, Ward CD, McLellan DL.** Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases [Letter]. J Neurol Neurosurg Psych. 1997;62:198.
37. **Brin MF.** Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve. 1997;S6:146-68.
38. **Cole LA.** The specter of biological weapons. Sci Am. 1996;275:60-5.
39. **Ekeus R.** Report of the Secretary General on the status of the implementation of the Special Commission's plan for the ongoing monitoring and verification of Iraq's compliance with relevant parts of Sector C of Security Council Resolution 687. New York: United Nations Special Commission (UNSCOM); 1991.
40. **Danzig R.** Biological warfare: a nation at risk—a time to act. Strategic Forum. 1996;58:1-4.
41. **Woodruff BA, Griffin PM, McCroskey LM, Smart JF, Wainwright RB, Bryant RG, et al.** Clinical and laboratory comparison of botulism from toxin types A, B, and E in the United States, 1975-1988. J Infect Dis. 1992;166: 1281-6.
42. **Hughes JM, Blumenthal JR, Merson MH, Lombard GL, Dowell VR Jr, Gangarosa EJ.** Clinical features of types A and B food-borne botulism. Ann Intern Med. 1981;95:442-5.
43. **Centers for Disease Control and Prevention.** Botulism in the United States, 1899-1973: Handbook for Epidemiologists, Clinicians, and Laboratory Workers. Atlanta: Centers for Disease Control; 1978:3. Publication no. (CDC) 74-8279/G.
44. **Duchen LW.** An electron microscopic study of the changes induced by botulism toxin in the motor end-plates of slow and fast skeletal muscle fibres of the mouse. J Neurol Sci. 1971;14:47-60.
45. **Tsujihata M, Kinoshita I, Mori M, Mori K, Shirabe S, Satoh A, et al.** Ultrastructural study of the motor end-plate in botulism and Lambert-Eaton myasthenic syndrome. J Neurol Sci. 1987;81:197-213.
46. **Merson MH, Dowell VR Jr.** Epidemiologic, clinical and laboratory aspects of wound botulism. N Engl J Med. 1973;289:1105-10.
47. **Hatheway CL.** Botulism: the present status of the disease. In: Montecucco C, ed. Clostridial Neurotoxins. Current Topics in Microbiology and Immunology. v 195. New York: Springer; 1995:55.
48. **Wilson R, Morris JG Jr, Snyder JD, Feldman RA.** Clinical characteristics of infant botulism in the United States: a study of the non-California cases. Pediatr Infect Dis. 1982;1:148-50.
49. **Arnon SS.** Infant botulism. In: Feigen RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases. 4th ed. Philadelphia: WB Saunders; 1998:1570-7.
50. **Spika JS, Shaffer N, Hargrett-Bean N, Collin DS, MacDonald KL, Blake PA.** Risk factors for infant botulism in the United States. Am J Dis Child. 1989;143:828-32.
51. Botulism—United States, 1978. MMWR Morb Mortal Wkly Rep. 1979;28: 73-5.
52. **Griffin PM, Hatheway CL, Rosenbaum RB, Sokolow R.** Endogenous antibody production to botulism toxin in an adult with intestinal colonization botulism and underlying Crohn's disease. J Infect Dis. 1997;175:633-7.
53. **McCroskey LM, Hatheway CL.** Laboratory findings in four cases of adult botulism suggest colonization of the intestinal tract. J Clin Microbiol. 1988; 26:1052-4.
54. **Chia JK, Clark JB, Ryan CA, Pollack M.** Botulism in an adult associated with food-borne intestinal infection with *Clostridium botulinum*. N Engl J Med. 1986;315:239-41.
55. **St Louis ME.** Botulism. In: Evans AS, Brachman PS, eds. Bacterial Infections of Humans: Epidemiology and Control. 2d ed. New York: Plenum Medical; 1991:115.
56. **Hatheway CL.** Botulism. In: Balows A, Hausler WH, Lennette EH, eds. Laboratory Diagnosis of Infectious Diseases: Principles and Practice. v 1. New York: Springer-Verlag; 1988:111.
57. **Hatheway CL, Ferreira JL.** Detection and identification of *Clostridium botulinum* neurotoxins. In: Singh BR, Tu AT, eds. Natural Toxins II: Proceedings of a Symposium. 209th American Chemical Society National Meeting, Anaheim, CA, 2–7 April 1995. New York: Plenum; 1996:481-98.
58. **Szabo EA, Pemberton JM, Gibson AM, Eyles MJ, Desmarchelier PM.** Polymerase chain reaction for detection of *Clostridium botulinum* types A, B, and E in food, soil and infant faeces. J Appl Bacteriol. 1994;76:539-45.
59. **Dowell VR Jr, McCroskey LM, Hatheway CL, Lombard GL, Hughes JM, Merson MH.** Coproexamination for botulinal toxin and *Clostridium botulinum*. A new procedure for laboratory diagnosis of botulism. JAMA. 1977; 238:1829-32.
60. **Hatheway CL, Snyder JD, Seals JE, Edell TA, Lewis GE Jr.** Antitoxin levels in botulism patients treated with trivalent equine botulism antitoxin to toxin types A, B, and E. J Infect Dis. 1984;150:407-12.
61. **Black RE, Gunn RA.** Hypersensitivity reactions associated with botulinal antitoxin. Am J Med. 1980;69:567-70.
62. **Tacket CO, Shandera WX, Mann JM, Hargrett NT, Blake PA.** Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. Am J Med. 1984;76:794-98.-