

Outline

Agent
Epidemiology
Clinical Features
Differential Diagnosis
Laboratory Diagnosis
Treatment and Prophylaxis
Infection Control
References

By law, health care providers must report suspected or confirmed Botulism to the local health department immediately (within 1 hr).

Even a single case of Botulism is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

AGENT

Botulism is an intoxication caused by botulinum toxin, which is produced by *Clostridium botulinum* and, rarely, by other *Clostridium* species.

Organism. *Clostridium botulinum* is a gram-positive, strictly anaerobic, spore-forming bacillus commonly isolated from soil and from marine and lake sediments. There are several strains, all of which elaborate toxin. *C. botulinum* bacteria are not, in and of themselves, toxic to humans; disease is caused by exposure to the bacterial toxin.

Toxin. There are seven serotypes of the toxin, labeled A through G. Types A, B, and E (and rarely, F) cause natural disease in humans. Botulinum toxins are colorless, odorless and tasteless, and are the most lethal toxins known, causing death at doses of <1 mcg. The toxin is inactivated by heating to 100°C for 1 minute, 85°C for 5 minutes, or 80°C for 20 minutes. Antibiotics have no activity against the toxin itself.

Spores. In response to unfavorable environmental conditions (changes in pH, temperature, and water or nutrient availability), *C. botulinum* bacteria "sporulate" – i.e. they become dormant, do not reproduce, and alter their cellular processes to increase resistance to chemicals, heat, air, and drying. Thus, *C. botulinum* spores are hardy, resistant to dessication, heat, UV light, and alcohols, and can survive boiling for up to 4 hours. (They are, however, readily killed by chlorine solutions.) Once the spores encounter more favorable conditions, such as are found in contact with human tissues, they will "germinate," thereby producing growing cells that are capable of reproducing and elaborating toxin.

Botulinum Toxin as a Biological Weapon

Several countries, including the the USA, the Soviet Union, Japan, and Iraq have conducted research on use of botulinum toxin as a biological weapon and may have stockpiled weapons containing it. Likely modes of dissemination for toxin used as a weapon include:

- **Deliberate contamination of food or beverages.** Food or beverage items that are possible vehicles for botulinum toxin are those which are not heat-processed at 85°C (185°F) for 5 minutes before consumption, and those which are appropriately heat-processed but then become contaminated sometime after processing has occurred. Thus, even at typical pasteurization temperatures (74°C/165°F for 30 seconds), some of the toxin would remain intact.
- **Dispersion of aerosolized toxin.** Animal studies and rare cases of laboratory accidents have confirmed the pathogenicity of aerosolized toxin. Experts have estimated that 1 gm of aerosolized botulinum toxin could kill up to 1.5 million people, though technical factors would make such dissemination difficult.
- **Contamination of a water supply.** This is possible but felt to be unlikely due to the large amount of toxin needed to contaminate a water supply. Also, toxin is rapidly inactivated by standard drinking water treatment, and is naturally inactivated in fresh water within 3 to 6 days.

The following features of a botulism outbreak would suggest deliberate toxin release:

- **An outbreak involving a large number of cases**
- **An outbreak caused by an unusual toxin type (C, D, F, or G) or involving type E toxin without an apparent aquatic source**
- **Multiple simultaneous outbreaks with or without an apparent source**
- **Cases lack a common food exposure, but were in geographic proximity during the week before symptom onset (suggests aerosol release)**

Naturally Occurring Botulism

Naturally occurring botulism is a rare disease with an annual incidence of approximately 100 cases in the USA.

Food-borne botulism is caused by ingestion of food contaminated with preformed botulinum toxin. In order for food-borne botulism to occur, the food item must be contaminated with *C. botulinum* spores, the spores must survive food preservation methods and then germinate and produce toxin under anaerobic, low-acid, warm conditions. Finally the food must not be reheated sufficiently to inactivate the heat-labile toxin before the food is consumed ($\geq 85^{\circ}\text{C}$ for 5 minutes). Toxin types A, B, and E account for most cases of foodborne botulism.

Between 1990 and 2000, there were a median of 14 food-borne botulism events annually in the USA, with a median of 1 case per event. From 1994-2003 there were 30 cumulative cases of food-borne botulism reported in California, none occurring in San Francisco. Food-borne botulism (especially type E) is a significant public health problem among Alaskan natives due to consumption of fermented meat from aquatic mammals and fish.

Wound botulism is caused by infection of a contaminated wound with *C. botulinum* organisms, and subsequent absorption into the circulation of locally produced toxin. Most cases are related to injection drug use. In 2004, wound botulism was reported among 8 injection drug users in San Francisco, in association with use of black tar heroin.

Infant botulism is caused by ingestion of *C. botulinum* spores. The spores colonize the GI tract, germinate, and produce toxin which is absorbed into the circulation. The source of spores typically is unknown, although ingestion of corn syrup or raw honey accounts for some cases. From 1994-2003 there were 283 cumulative cases of infant botulism reported in California, none occurring in San Francisco. Intestinal botulism similar to that in infants has been reported very rarely in adults.

Inhalational botulism does not occur in nature, but has been produced experimentally in laboratory animals. Three human cases occurred in 1962 in lab technicians working with aerosolized botulinum toxin.

Botulinum toxin is also used therapeutically. Purified, highly diluted, injectable botulinum toxin is used to treat a range of spastic or autonomic muscular disorders such as cervical dystonia and strabismus (toxin type B). Toxin type A is used in extremely minute doses for the treatment of facial wrinkles (Botox®). Systemic effects of the toxin have been noted very rarely after medical use or misuse of the product.

CLINICAL FEATURES

Botulism is caused by exposure to botulinum toxin. Exposure to toxin may occur through several mechanisms:

- Ingestion of preformed toxin (food-borne)
- Inhalation of preformed toxin
- Local production of toxin by *C. botulinum* organisms in the GI tract (infant; intestinal)
- Local production of toxin by *C. botulinum* organisms in devitalized tissue (wound)

Regardless of the route of intoxication the same neurologic syndrome develops. Botulinum toxin acts at the neuromuscular junction of skeletal muscle neurons and cholinergic autonomic synapses. It binds irreversibly to presynaptic receptors to inhibit the release of acetylcholine. The effect lasts weeks to months, until the synapses and axonal branches regenerate. Death from botulism results acutely from airway obstruction or paralysis of respiratory muscles.

Botulism is characterized by acute afebrile descending symmetric paralysis. Disease generally begins with cranial nerve dysfunction and then progresses to muscle weakness, with the proximal muscle groups involved first.

Severity of disease is variable, ranging from mild cranial nerve dysfunction to complete flaccid paralysis. Both the severity of disease and the rapidity of onset correlate with the amount of toxin absorbed into the circulation.

BOTULISM: CLINICAL FEATURES	
Incubation Period	<ul style="list-style-type: none"> • 12-72 hours (range 2 hrs - 8 days) • Dependent on dose of toxin
Signs & Symptoms	<p>Early Presentation – cranial nerve abnormalities</p> <ul style="list-style-type: none"> • Dysarthria • Blurred and/or double vision • Dry mouth • Ptosis • Symptoms may be slow in onset or rapidly progressive (dose-dependent) <p>Later Presentation – descending paralysis</p> <ul style="list-style-type: none"> • Dysphonia, dysphagia • Symmetrical, descending progressive muscular weakness • Dilated or fixed pupils • Decreased gag reflex • Respiratory failure • Autonomic nerve dysfunction; may include urinary retention, orthostasis • Normal mental status, though may appear lethargic and have difficulty with communication • Normal sensory nerve function • Afebrile unless there is complicating infection
Laboratory Findings	<ul style="list-style-type: none"> • Normal CSF glucose, protein, cell count • Normal CBC • Normal imaging of brain and spine (CT scan or MRI) <p>Characteristic EMG findings include:</p> <ul style="list-style-type: none"> • Incremental response (facilitation) to repetitive stimulation at 50 Hz • Short duration of motor unit potentials • Normal sensory nerve function • Normal nerve conduction velocity

DIFFERENTIAL DIAGNOSIS

Botulism is frequently misdiagnosed. A high index of suspicion is necessary for early presumptive diagnosis as there are no readily available rapid confirmatory tests. Diagnosis is primarily made on the basis of clinical presentation and epidemiologic evidence of potential exposure. However it must be recognized that in the event of bioterrorist attack, the source of exposure may be unclear.

Important questions to ask:

- Recent history of eating home-canned vegetable, fruit, and fish products
- Other known individuals with similar symptoms
- Recent travel to Alaska or consumption of Alaskan seafood products
- Recent history of IVDU, particularly with black tar heroin or cocaine

Key features that distinguish botulism are the constellation of:

- **Descending paralysis**
- **Cranial nerves prominently involved**
- **Symmetric bilateral impairment**
- **Normal CSF studies**
- **Characteristic EMG findings**
- **Absence of paresthesias**
- **Afebrile illness**
- **Normal mental status**

Other conditions to consider:

- Guillain-Barre syndrome (particularly Miller-Fisher variant)
- Myasthenia gravis
- Stroke
- Intoxication with CNS depressants
- Lambert-Eaton syndrome
- Diabetic neuropathy
- Sudden infant death syndrome
- Magnesium intoxication
- Tick paralysis
- Poliomyelitis
- CNS infections, particularly of brainstem
- CNS tumor
- Psychiatric illness (i.e. conversion paralysis)
- Inflammatory myopathy
- Paralytic shellfish poisoning

LABORATORY DIAGNOSIS

Diagnosis is primarily made on the basis of clinical presentation. Laboratory confirmation can be achieved in most cases by detection of botulinum toxin in serum via mouse bioassay, in which mice are injected with the patient sample and observed for the development of characteristic symptoms. Detection of toxin is dependent on the total dose of toxin absorbed and the time from symptom onset to testing.

The mouse test is able to detect fractional nanogram amounts of toxin. The test requires 1-4 days to complete and is performed only at reference laboratories. Test results may be negative if the samples were collected late or the quantity of toxin is small; thus lack of detection of botulinum toxin does not necessarily rule out the diagnosis of botulism. Tests other than the mouse bioassay are currently investigational.

If you are testing or considering testing for Botulism, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830). SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.**

For mouse bioassay, obtain at least 30 cc of serum. (If directed by public health personnel, obtain 20-50 cc of stool, enema fluid and/or gastric aspirate.) Serum specimens must be taken before antitoxin treatment in order to demonstrate the presence of botulinum toxin. The lab should be notified if the patient has received Tensilon or "stigmine" drugs prior to testing. Serum, stool, and gastric specimens should be kept refrigerated, not frozen.

Potentially contaminated food samples may be collected (10-50 gm), sealed, and transported under refrigeration. Environmental specimens with potential contamination may be collected (soil, 50-100 gm; water >100 cc) and transported at room temperature.

In case of suspected inhalational exposure, toxin may be present in nasal mucosa for up to 24 hours. However the utility of nasal sampling is unknown.

Routine laboratory tests on serum and CSF are generally within normal limits unless a secondary process has occurred. Cultures of blood, stool, sputum, and urine are not helpful in confirming a diagnosis of botulism. Viable organisms are generally present only in wound or infant botulism. Patients do not generally develop an antibody response due to the sub-immunogenic amount of toxin necessary to produce disease.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Supportive care, including mechanical ventilation and parenteral nutrition, and timely administration of botulinum antitoxin are the mainstays of care for botulism. Ventilatory support may be required for several weeks or more. With modern intensive care methods, case-fatality rates for botulism in the USA have dropped to <10%.

Note: aminoglycosides and clindamycin are contraindicated for treatment of secondary infections since they may exacerbate the neuromuscular blockade.

Antitoxin Treatment

To obtain antitoxin, phone SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830). If the clinical picture is compatible with botulism, antitoxin may be released emergently.

Antitoxin is most effective when given within 24 hours after symptom onset. It cannot reverse any existing paralysis. However it binds to any toxin remaining in the circulation and can slow progression of further disease and potentially decrease the duration of ventilatory support and increase the likelihood of survival.

Antitoxin is provided by the CDC but is available for release only via state and local health departments. Once antitoxin is requested, it generally can be delivered within 12 hours. The currently available formulation is botulinum antitoxin bivalent for types A and B (licensed by FDA). Botulinum antitoxin type E is investigational. A trivalent preparation (types A, B, E) has been discontinued. The military is testing a heptavalent antitoxin (type A through G).

One 10-ml vial of each preparation of antitoxin is sufficient to neutralize circulating toxin from most naturally occurring intoxications. A repeat dose is not usually necessary.

Since antitoxin is of equine origin, hypersensitivity reactions, including anaphylaxis, serum sickness, and febrile reactions have occurred in up to 9% of patients receiving antitoxin. Skin testing for hypersensitivity should be performed in all patients before administering antitoxin. If skin testing is positive, the patient can be desensitized over several hours before the full dose of antitoxin is administered. Diphenhydramine and epinephrine should be available during administration.

No Prophylaxis of Exposed, Asymptomatic Persons

An exposed person is defined as a person who has been directly exposed to botulinum neurotoxin. In the case of a bioterrorist event, the exposure would most likely occur by inhalation of toxin.

There is currently no available post exposure prophylaxis for asymptomatic exposed persons. Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur. As there is no prophylactic measure for botulism exposure other than observation and early treatment in the event of symptoms, exposed persons and their families may experience anxiety and/or somatic symptoms that may include neurologic symptoms. These patients should be carefully assessed. Antitoxin supplies are limited, and therapy will be reserved for patients with compatible neurological findings.

Pre-exposure immunization with botulinum toxoid is restricted to certain laboratory and military personnel. Supplies are extremely limited and would not be available for the public.

INFECTION CONTROL*

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Person-to-person transmission does not occur. **Standard Precautions** are adequate for the care of patients with botulism. Patients do not require isolation.

* For description of Precautions, see chapter on Infection Control

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