INTRODUCTION

Botulism is a disease caused by exposure to botulinum toxin produced from Clostridium species, mainly Clostridium botulinum. Clinical forms of the disease include foodborne, inhalational, wound, infant, adult intestinal toxemia, and iatrogenic. C. botulinum is a gram-positive, strictly anaerobic, spore-forming bacillus naturally found in soil and aquatic sediments. There are seven types of the toxin based on antigenic differences, labeled A through G. Types A, B, and E (and rarely, F) are pathogenic in humans. Types C, D, and E cause illness in other mammals, birds, and fish. Botulinum toxin lacks color, odor, and taste and is the most lethal toxin known. Death is caused by doses of less than 1 µg. Antibiotics have no activity against the toxin itself.1-3

In response to unfavorable environmental conditions (changes in pH, temperature, and water or nutrient availability), C. botulinum bacteria sporulate. C. botulinum spores are hardy, resistant to dessication, heat, ultraviolet (UV) light, and alcohols, and can survive boiling for up to 4 hours; however, they are readily killed by chlorine-based disinfectants. Once spores encounter more favorable conditions, such as are found in contact with human tissues, they germinate, thereby producing growing cells that are capable of reproducing and elaborating toxin.1-3

The Working Group for Civilian Biodefense considers botulism to be a dangerous potential biological weapon because of the pathogen’s “extreme potency and lethality; its ease of production, transport, and misuse; and the need for prolonged intensive care among affected persons.” Use of botulism as a biological weapon is expected to produce severe medical and public health outcomes.3-6
Botulinum Toxin as a Biological Weapon
State-sponsored military programs have researched and weaponized botulinum toxin dating back to the 1930s. Botulism has also been used as a weapon by a terrorist group. Unfortunately, botulism is ubiquitous in nature and therefore access to it cannot be easily controlled.3, 4

Likely modes of dissemination for toxin used as a weapon include:3-6

- **Contamination of food or beverages.** Possible food or beverage vehicles for botulism toxin are those that are not heated at 85°C (185°F) for 5 minutes before consumption or those that are contaminated after appropriate heating. Typical pasteurization does not remove all toxin.

- **Dispersion of aerosolized toxin.** Animal studies and rare cases of laboratory accidents have confirmed the pathogenicity of aerosolized toxin. One study estimates that aerosolizing 1 g of botulinum toxin could kill up to 1.5 million people; while another estimates that a point source exposure could kill 10% of the population 500 meters downwind. Technical factors make such dissemination difficult.

- **Contamination of a water supply.** This is a possibility, but not likely because of the quantity of toxin needed to effectively contaminate a water supply. Additionally, standard drinking water treatment inactivates the toxin quickly and, in fresh water, it is inactivated through natural mechanisms in 3 to 6 days.

An intentional release of botulinum toxin would have the following characteristics:3, 4, 6

- Clustering in time: multiple similarly presenting cases of rapidly progressing acute flaccid symmetric paralysis with prominent bulbar palsies, generally 12 to 36 hours after release
- Atypical host characteristics: cases of unusual botulinum toxin type (C, D, F, G, and possibly E) or cases without typical gastrointestinal symptoms of nausea, vomiting, and diarrhea
- Unusual geographic clustering: cases in geographic proximity during the week before symptom onset, but lack common food exposure (aerosol exposure) or toxin type outside of typical geographic range
- Absent risk factors: multiple outbreaks without an association with a common food source

Naturally Occurring Botulism

**Reservoirs**
The sporulated form of the bacterium is commonly found in soils and aquatic sediments. Cistern water, dust and foods, including honey, can become contaminated from contact with the soil.1, 2, 7

**Mode of Transmission**
Botulism is caused by exposure to botulinum toxin. Humans can become infected in a number of ways:

- Inhalation of toxin (inhalational)
• Consumption of toxin (foodborne)
• Consumption of *C. botulinum* spores (infant; adult intestinal toxemia)
• Contamination of a tissue with *C. botulinum* spores (wound)
• Contamination of a tissue with toxin (iatrogenic)

**Worldwide occurrence**
In the late 1700s, botulism emerged as a disease because of changes in sausage production in Europe. In fact, *botulus* means sausage. Soon thereafter in the early 1800s, botulism associated with consumption of fermented fish was recognized in Russia. Wound and infant botulism were discovered much later in the mid to late 1900s. In 1999-2000, more than 2500 cases of foodborne botulism were reported in Europe. The highest incidence is found in countries of the former Soviet Union and in Asia and is related to improper food handling. Type B is more common in Europe, whereas type E is more common in Scandinavia and Canada and is frequently linked to improper storage of fish and marine mammals.¹,⁸

**United States Occurrence**
In the United States, naturally occurring botulism is a rare disease with an annual incidence of approximately 100 cases (infant: 71; food: 24; and wound: 3).⁹ More than half of foodborne cases occur in the Western states of California, Oregon, Washington, Alaska, and Colorado.⁹ Type E is more common among Alaskan natives because of their diet of fermented meat from aquatic mammals and fish.¹⁰ Type A is found mainly in Western states and type B is more common in the East.¹ Most cases of wound botulism result from injection drug use with black tar heroin, which is more common in the Western states.¹¹

**Occurrence in California and San Francisco**
From 1994 to 2006, 44 cases of foodborne botulism were reported in California, and one of these occurred in San Francisco.¹²-¹⁵

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**CLINICAL FEATURES**

Regardless of the route of intoxication the same clinical neurologic syndrome develops.¹⁻³,¹⁶ Botulism is an afebrile descending symmetric paralytic illness. Disease generally begins with absorption of toxin by mucosal surfaces in the gastrointestinal system, the eye or nonintact skin. Cranial nerve dysfunction ensues followed by muscle weakness beginning with the proximal muscle groups. Severity of disease is variable, ranging from mild cranial nerve dysfunction to flaccid paralysis. Both the severity of disease and the rapidity of onset correlate with the amount of toxin absorbed into the circulation.³,⁶

Botulinum toxin blocks acetylcholine release at the neuromuscular junction of skeletal muscle neurons and peripheral muscarinic cholinergic autonomic synapses. It binds irreversibly to presynaptic receptors to inhibit the release of acetylcholine and cause neuromuscular weakness and autonomic dysfunction. 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.¹⁻³
The case fatality rate was close to 60% prior to the advent of critical care. Even today, the mortality rate is high if treatment is not immediate and proper. In an outbreak setting, the mortality rate for the first case is 25% and for all other cases is 4%. A shorter incubation period has been linked to higher mortality, possibly reflecting a dose-dependent response. Fatality doubles in persons above the age of 60.1-3

**Food-borne botulism** occurs from the consumption of preformed botulinum toxin in food. Waterborne botulism has not been seen. Toxin types A, B, and E account for most cases of foodborne botulism. Minute amounts of toxin can cause disease. A case in which a contaminated potato was spit out before being swallowed, resulted in 6 months of hospitalization.

In order for foodborne botulism to occur:1, 8
- *C. botulinum* spores must contaminate the food
- anaerobic, nonacidic, low sugar and salt, and warm conditions must be met during the food preservation so that the spores can survive, germinate and produce toxin
- the food must not be reheated sufficiently to inactivate the heat-labile toxin before the food is consumed (>85°C for 5 minutes).

**Inhalational botulism** does not occur in nature; however three human cases occurred in 1962 in lab technicians working with aerosolized botulinum toxin. It has also been produced experimentally in laboratory animals.

**Wound botulism** is caused by toxin absorbed into the circulation through a wound. Most cases are related to injection drug use, especially in association with use of black tar heroin being injected into soft tissue ("skin popping").11

**Infant botulism** occurs from the consumption of *C. botulinum* spores. The spores invade the gastrointestinal tract, replicate, and release 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.

**Adult intestinal toxemia (or undefined) botulism** occurs from the consumption of *C. botulinum* spores. Characteristics include unknown source of toxin, presence of toxin in stool, and abnormal gastrointestinal pathology (e.g., Billroth surgery, Crohn's disease, and peptic ulcer disease) or antimicrobial drug use.

**Iatrogenic botulism** has been noted very rarely after medical use or misuse of the botulinum toxin. Purified, highly diluted, injectable botulinum toxin is used to treat a range of spastic or autonomic muscular disorders. Toxin type A (Botox) is used in extremely minute doses for the treatment of facial wrinkles and blepharospasm, cervical dystonia strabismus, glabellar lines, and primary axillary hyperhidrosis. Toxin type B (Myobloc, Neurobloc) is used to treat cervical dystonia. Dysphagia, limited paresis and other neuromuscular impairment of the toxin are symptoms that have been seen.17
### CLINICAL FEATURES: BOTULISM

<table>
<thead>
<tr>
<th>Incubation Period</th>
<th>12-80 hours (range 2 hours to 8 days)</th>
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<tbody>
<tr>
<td>Transmission</td>
<td>Inhalation of toxin</td>
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<td>Consumption of toxin or <em>C. botulinum</em> spores</td>
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<td></td>
<td>Contamination of a tissue with toxin or <em>C. botulinum</em> spores</td>
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<tr>
<td>Signs and Symptoms</td>
<td>Cardinal signs</td>
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<tr>
<td></td>
<td>• Afebrile</td>
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<td></td>
<td>• Symmetrical neurological manifestations</td>
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<td>• Normal mental status, though may appear lethargic and have difficulty with communication</td>
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<td></td>
<td>• Normal to slow heart rate without the presence of hypotension</td>
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<td>• Normal sensory nerve function, other than vision</td>
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<td>Early presentation – cranial nerve abnormalities</td>
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<td></td>
<td>• Fatigue and vertigo</td>
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<td>• Double and blurred vision, intermittent ptosis and disconjugate gaze</td>
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<td>• Difficulty swallowing food</td>
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<td>Later presentation – descending paralysis</td>
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<td></td>
<td>• Difficulty moving eyes and mild pupillary dilation and nystagmus</td>
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<td></td>
<td>• Tongue weakness, decreased gag reflex, indistinct speech, dysphagia, dysphonia</td>
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<td></td>
<td>• Symmetrical, descending progressive muscular weakness, especially arms and legs</td>
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<td>• Unsteady gait</td>
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<td></td>
<td>• Extreme weakness, including postural neck muscles and occasional mouth breathing</td>
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<td>• Autonomic nerve dysfunction; may include urinary retention, orthostasis</td>
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<td></td>
<td>• Constipation</td>
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<td>Ingestional:</td>
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<td></td>
<td>• Dry mouth and dysarthria</td>
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<td>• Nausea and vomiting, except when exposure is purified toxin</td>
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<td></td>
<td>Inhalational:</td>
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<td></td>
<td>• Mucus in throat</td>
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<td></td>
<td>• Serous nasal discharge, salivation</td>
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<td>Infant:</td>
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<td>• Inability to suck and swallow</td>
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<td>• Constipation</td>
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<td></td>
<td>• Weakened voice</td>
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<td>• Floppy neck</td>
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<tr>
<td>Progression and Complications</td>
<td>Respiratory failure and possible aspiration pneumonia</td>
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<td></td>
<td>• Residual fatigue, dry mouth or eyes, dyspnea on exertion several years later</td>
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<tr>
<td>Laboratory and Radiographic Findings</td>
<td>Normal CSF values</td>
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<td></td>
<td>• Normal CBC</td>
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<td>• Normal imaging of brain and spine (CT scan or MRI)</td>
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<td>Characteristic EMG findings include:</td>
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<td>• Decremented response to repetitive nerve stimulation at low frequency (3 Hz)</td>
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<td>• Facilitated response to repetitive nerve stimulation at high frequencies (10-50 Hz)</td>
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<td>• Low compound muscle action potentential</td>
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CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomographic; EMG, electromyogram; MRI, magnetic resonance imaging.
DIFFERENTIAL DIAGNOSIS

Diagnosis of botulism during the initial stages requires a high index of suspicion because of the lack of readily available rapid confirmatory tests.

Important questions to ask include:

- recent history of eating
  - home-canned or home-prepared vegetable, fruit, including foil-wrapped baked potato
  - lightly preserved or fermented meat and fish products, including seafood products from Alaska, Canada or the Great Lakes
- other known individuals with similar symptoms
- recent history of injection drug use, particularly with black tar heroin or cocaine

Key features that distinguish botulism are the constellation of:

- afebrile illness
- normal mental status
- cranial nerves prominently involved
- descending paralysis
- symmetric bilateral impairment
- absence of paresthesias
- normal CSF studies
- characteristic EMG findings

Other conditions to consider are:

- Guillain-Barre syndrome (especially Miller-Fisher syndrome)
- myasthenia gravis
- stroke or CNS tumor
- CNS infections (particularly of brainstem)
- Lambert-Eaton syndrome
- tick paralysis
- sudden infant death syndrome
- hyperemesis gravidarum
- saxitoxin (paralytic shellfish poisoning)
- tetrodotoxin (puffer fish poisoning)
- laryngeal trauma
- diabetic neuropathy
- poliomyelitis/West Nile acute flaccid paralysis
- psychiatric illness (i.e., conversion paralysis)
- inflammatory myopathy
- streptococcal pharyngitis
- viral syndrome
- hypothyroidism
- overexertion
- diphtheria
- Wernicke's encephalopathy
- intoxication with CNS depressants (atropine, aminoglycoside, magnesium, ethanol, organophosphates, nerve gas, carbon monoxide)
LABORATORY DIAGNOSIS

Routine laboratory and radiographic findings for specific clinical presentations of botulism are listed in the clinical features table.

Although laboratory confirmation should be initiated as soon as possible if testing facilities are available, the clinical presentation should guide clinical management and public health interventions. Laboratory confirmation is challenging, but can be achieved in most cases by detection of botulinum toxin in serum, respiratory secretions, and stool via mouse bioassay, in which mice are injected with the patient sample and observed for the development of characteristic symptoms. Serum specimens must be taken before antitoxin treatment to demonstrate the presence of botulinum toxin. The test requires 1-4 days to complete and is performed only at reference laboratories. Electromyography provides diagnostic information more rapidly. Repetitive nerve stimulation at 20 to 50 Hz differentiates between various etiologies of acute flaccid paralysis. Electromyography is not recommended for infants.3, 6, 16

Because the laboratory diagnosis of botulism may take several days to complete, health department officials can authorize the release of antitoxin prior to laboratory confirmation on the basis of clinical findings and may be able to provide other rapid detection tests that are currently investigational (e.g., time-resolved fluorescence assay, toxin micronanosensor, ganglioside-liposome immunoassay, enzyme-linked immunosorbent assay [ELISA]).

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.sfcdcp.org).

Treatment
Outcome is based on early diagnosis and treatment. Supportive care (including airway protection, mechanical ventilation, and feeding by central tube or parenteral nutrition) and timely administration of equine botulinum antitoxin are keys to the successful management of botulism.2–3, 18 Establish a means of communication early because sometimes conditions such as debilitating headaches are not communicated after the onset of paralysis.

Antitoxin
Antitoxin administration should not be delayed for laboratory confirmation because antitoxin does not reverse disease or existing paralysis, but only stops progression of disease.

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.
- Inform your lab that botulism is under suspicion.
Patients given antitoxin within the first 24 hours after symptom onset had shorter hospital stays, shorter duration of ventilatory support, and a lower fatality rate (10%) than those given antitoxin more than 24 hours after onset (15%) or those who did not receive antitoxin at all (46%). 19, 20

Antitoxin is provided by the Centers for Disease Control and Prevention (CDC) but is available for release only by the state or local health departments. Delivery can be expected within 12 hours of request.

Consult public health authorities regarding dosage, because recommendations change. Currently, the CDC recommends immediate intravenous administration of the trivalent antitoxin (one vial diluted 1:10 over 30 minutes). If it is suspected that the exposure was to an extremely high dosage of toxin, the serum may be tested after treatment for the presence of remaining toxin. 16

Because antitoxin is of equine origin, hypersensitivity reactions can occur. From 1967 to 1977, 9% of persons treated with botulinal antitoxin had a nonfatal hypersensitivity reaction. 21 In recent years, when the recommended dosage has decreased 2- to 4-fold, less than 1% have experienced hypersensitivity reactions. 2 A skin test may be valuable in patients with allergies, previous anaphylaxis, or prior receipt of equine antitoxins. If skin testing is positive, consider desensitizing over several hours before administering the complete dose of antitoxin or pretreat with antihistamines, steroids, and epinephrine infusions. Diphenhydramine, epinephrine, and airway equipment should be easily accessible during any administration.

Human botulism immune globulin is used to treat infants, which is administered intravenously. 22

**Supportive care**

Ventilatory support may be required for several weeks or more. One study found the mean time on a ventilator for botulism cases was 58 days. 20

With modern intensive care methods, case fatality rates for botulism in the United States have dropped to less than 10%. In a mass casualty setting, measurement and management of ventilatory function may pose challenges because of limited ventilator capacities. Local health departments can request supplemental laryngoscopes, endotracheal tubes, and Ambu bags from the CDC. If personnel are limited, consider recruiting health civilians for bag ventilation.

A reverse Trendelenburg positioning with cervical vertebral support has been beneficial in terms of respiratory mechanics and airway protection in nonventilated infants with botulism, but has not been tested in adults. In adults, especially those with obesity, a 20- to 25-degree angle may be beneficial. 3

Utilize physical therapy and physical turning to minimize intensive care complications.

**Secondary infections**

Antibiotics may be used for treatment of secondary infections; however, aminoglycosides and clindamycin are contraindicated because they may exacerbate the neuromuscular blockade. 3
Post-exposure prophylaxis
There is currently no available postexposure prophylaxis for asymptomatic exposed persons.\textsuperscript{3, 16} Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur. Not all exposed persons will develop clinical 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.

Vaccine
Preexposure immunization with botulinum toxoid is restricted to certain laboratory and military personnel. Supplies are extremely limited and would not be available for the public.\textsuperscript{3, 16}

COMPLICATIONS AND ADMISSION CRITERIA

In patients with botulism, cranial nerve dysfunction progresses inexorably to a symmetric, descending muscle weakness or paralysis. Respiratory failure occurs in 40-70\% of botulism patients because of declining upper airway and ventilatory muscle strength. Additional complications of botulism include secondary infection of the respiratory system and sequelae related to intubation and mechanical ventilation, prolonged immobilization, and autonomic dysfunction. Diminished respiratory muscle function and easy fatigability were described by botulism patients 2 years after recovery.

Hospital admission is required for protection of the airway, mechanical ventilatory support, and fluid and nutritional management until normal muscular function returns.

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.sfcdcp.org).

Clinicians should notify local public health authorities and their laboratory of any suspected botulism case. Health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public. Both HICPAC (Hospital Infection Control Practices Advisory Committee) of the CDC and the Working Group for Civilian Biodefense recommend Standard Precautions for botulism patients in a hospital setting without the need for isolation. Person-to-person transmission does not occur.\textsuperscript{3, 16, 23}

Decontamination
After exposure to toxin, wash clothes and skin with soap and water. Inactivation of the toxin in the environment can take 2 days; however, changes in temperature and humidity can affect the rate of decomposition. Contaminated surfaces and spills of cultures or toxin can be disinfected with
sodium hypochlorite (0.1% which is a 1:50 dilution of household bleach) or sodium hydroxide (0.1N). Moist heat at 120°C for at least 15 minutes destroys spores.3

PEARLS AND PITFALLS

1. Botulism is often misdiagnosed as a polyradiculopathy (Guillain-Barre syndrome or Miller-Fisher syndrome), myasthenia gravis, or other diseases of the central nervous system. Botulism is distinguished from other flaccid paralyses by its initial presentation with prominent cranial neuropathy, its subsequent descending, symmetrical paralysis, and its absence of sensory nerve deficits.

2. In the United States, botulism is more likely than Guillain-Barre syndrome, chemical poisoning, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis.

3. Botulism antitoxin neutralizes freely circulating toxin but does not dislodge toxin already bound to presynaptic receptors. Early administration of antitoxin can help to inhibit further paralysis, but does not reverse paralysis that has already occurred.

4. Botulism antitoxin is limited in quantity and is available only through public health authorities. Since the laboratory diagnosis of botulism requires an in-vivo assay and may take several days to complete, health department officials often authorize the release of antitoxin prior to laboratory confirmation, on the basis of clinical findings.

REFERENCES


