

SANTA CRUZ COUNTY HEALTH SERVICES AGENCY

Medical Treatment and Response to Suspected Botulism: Information for Health Care Providers During Biologic Emergencies

OCTOBER 2001

- I. Key Summary Points
 - II. Introduction/Epidemiology
 - III. Significance as a Potential Bioterrorism Agent
 - IV. Clinical Manifestations
 - V. Laboratory Diagnosis
 - VI. Handling Laboratory Specimens
 - VII. Treatment
 - VIII. Isolation of Patients
 - IX. Disposal of Infectious Waste
 - X. Autopsy and Handling of Corpses
 - XI. Management of Exposed Persons
 - XII. Reporting
 - During Business Hours
 - After Business Hours
 - XIII. References
-

**ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO
SANTA CRUZ COUNTY HEALTH SERVICES AGENCY, DISEASE CONTROL:**

During Business Hours:

831-454-4114

After Hours (Nights, Weekends and Holidays):

831-471-1183

I. KEY SUMMARY POINTS

Epidemiology:

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- **Botulism is not transmitted from person to person**

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory

Patient Isolation:

- Standard precautions. Patients do not require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin is in limited supply and is available only from the Division of Communicable Disease Control, California Dept of Health Services

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE SANTA CRUZ COUNTY HEALTH SERVICES AGENCY, DISEASE CONTROL:

During Business Hours:

831-454-4114

After Hours (Nights, Weekends and Holidays):

831-471-1183

II. Introduction/Epidemiology

Botulism is a neuroparalytic disease caused by a neurotoxin produced by the anaerobic spore-forming bacterium, *Clostridium botulinum*. Two additional bacteria, *Clostridium barati* and *Clostridium butyricum*, can also occasionally produce botulinum toxin.

Botulinum toxins are designated A through G based on antigenic differences. Human botulism is caused by toxin types A, B, E and rarely, F; botulism associated with toxin type A is most severe. In the eastern United States, botulism is primarily caused by the botulinum toxin type B. Botulism is classically acquired by the ingestion of preformed neurotoxin, although botulism can also be caused by localized infection with C.

botulinum (wound botulism) or *C. botulinum* colonization of the intestine with in vivo toxin production (infant botulism).

Botulinum neurotoxins irreversibly bind to presynaptic receptors of peripheral nerves and subsequently inhibit release of acetylcholine. Both the neuromuscular junctions and cholinergic autonomic synapses are affected, resulting in skeletal muscle and bulbar paralysis. Recovery can take weeks to months, requiring the regeneration of presynaptic axons and formation of new synapses.

Botulism in the United States is now most commonly recognized as wound botulism, which develops as a complication of injecting drug use. Botulism can also present in small clusters or single cases related to home-canned foods or vegetables of low acidity (*e.g., beans, peppers, carrots and corns*). Recent examples of foodborne botulism due to non-preserved foods include foil-wrapped baked potatoes and sauteed onions. Foodborne botulism is always transmitted by foods that are not heated thoroughly before eating. In 1999, there were 26 cases of foodborne botulism and 41 cases of wound botulism reported in the U.S. Thirty eight of the 41 wound botulism cases were reported in California.

Airborne transmission of botulinum neurotoxin does not usually occur naturally, although three persons were infected by aerosolized toxin while disposing of rabbits and guinea pigs whose fur had been coated with previously aerosolized botulinum toxin during a laboratory accident in Germany in 1962. If used in a bioterrorist attack, aerosolization of preformed toxin would likely occur causing disease by the inhalation route. The clinical manifestations of disease would be identical to foodborne botulism, except for the absence of prodromal gastrointestinal symptoms. Deliberate contamination of food or water supplies is also possible.

Botulism is not transmitted by human-to-human contact.

An outbreak of botulism with the following characteristics should raise suspicion of a bioterrorist attack:

- An unusual toxin type for California
- Multiple, simultaneous cases with no common food exposure, no wounds, and no history of injecting drug use

- Absence of gastrointestinal prodromal symptoms would suggest an aerosolized route of exposure in patients with a clinical presentation compatible with botulism

III. Significance as a Potential Bioterrorist Agent

- Botulinum toxin is one of the most potent compounds known; it is 100,000 times more toxic than sarin.
- Could be released as an aerosol or used to contaminate water or food supplies.
- Iraq deployed 12,000 liters of botulinum toxin in over 100 munitions during the Gulf War in 1991.
- The Aum Shinrikyo cult released botulinum toxin during a failed bioterrorist attack in Japan.
- A massive outbreak of botulism would easily overwhelm both the existing supply of botulinum antitoxin and intensive care support (ventilator) capacity at acute care hospitals.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission. The clinical presentation would be similar for both the inhalational and foodborne routes of transmission, with the exception that inhalational botulism would not have prominent gastrointestinal prodromal symptoms.

Incubation period - typically 12-36 hours, can be several days (dose-dependent).

Inhalational botulism may have an incubation period up to 3 days.

Symptoms - Patients may exhibit some or all of the following signs or symptoms: These findings may appear in any order, the following represents the classical temporal relationship:

Early Symptoms (Cranial nerve abnormalities precede peripheral muscle weakness):

- blurred vision
- diplopia (double vision)

- dry mouth

Later Symptoms (more severe disease):

- dysphonia (hoarse voice)
- dysarthria (difficulty articulating words)
- dysphagia (difficulty swallowing)
- ptosis
- symmetrical, descending, progressive muscular weakness with fatiguability with repetitive muscle activity
- respiratory failure

The patient may have dilated or fixed pupils. Patients are typically alert and responsive and sensory deficits (other than blurred vision) do not occur. Deep tendon reflexes may be symmetrically depressed or remain normal. Fever does not occur unless there is a complicating infection.

The differential diagnosis of botulism includes myasthenia gravis and Lambert-Eaton myasthenic syndrome (lack autonomic features), tick paralysis (tick should be attached), acute inflammatory polyneuropathy (Guillain-Barre syndrome {GBS} usually begins with sensory complaints, rarely begins with cranial nerve abnormalities, and the progression of motor weakness may be ascending as opposed to the descending progression seen with botulism {except for the Miller-Fisher variant}; in addition, the CSF protein is usually elevated in GBS, although it may take 1 – 2 weeks to see an increase), polio (febrile illness with asymmetric weakness), magnesium intoxication and brain stem infarction.

The diagnosis of botulism requires a very high index of suspicion, and is most often based on epidemiologic evidence of a potential exposure. In the event of a bioterrorist attack, a recognized source of exposure may be absent. Clinical suspicion is of utmost importance.

V. Diagnosis

A. Laboratory

Laboratory diagnosis is made by mouse neutralization assay, which is performed only at the California Microbial Diseases Laboratory. If botulism is suspected, please call the Santa Cruz County Health Services Agency, Disease Control at 831-454-4114 to arrange for submission of specimens for testing. After hours call County Communications at 831-471-1183.

The diagnosis of botulism requires a compatible clinical syndrome. The detection of botulinum neurotoxin in the patient's serum and/or stool (in the case of food-borne botulism) serves to confirm the diagnosis. The detection of toxin will be dependent on the total dose absorbed and the time from onset of symptoms to testing. The specimens will be evaluated by mouse neutralization bioassay, currently the gold standard assay. This assay can detect as little as 0.03 ng of botulinum toxin.

- Processing of Specimens
 - Obtain serum (draw 30 cc in a tube with no anticoagulant, refrigerate until well-clotted, centrifuge and separate the serum into a sterile tube for transport), stool (at least 25 gm), and gastric aspirate if available. Immediately call the Santa Cruz County Health Services Agency, Disease Control at 831-454-4114 (831-471-1183 after hours) to arrange for testing.
 - Serum specimens must be taken *before* antitoxin treatment to demonstrate the presence of botulinum toxin.
 - In California, anti-toxin and laboratory testing for toxin are available only from the state Department of Health Services. The Santa Cruz County Health Services Agency Laboratory and Disease Control Program

facilitate routing of laboratory specimens and evaluation of need for anti-toxin.

- All specimens should be refrigerated, and not frozen, and examined as quickly as possible after collection. Freezing will hamper recovery of *Clostridium botulinum*, but will not prevent detection of toxin.
- Communication of Results
 - Toxin test results may take up to 4 days to complete after specimens are received. Results will be given by the Santa Cruz County Public Health Laboratory and Disease Control Program. The lack of detection of toxin in serum of patients with clinically compatible illness does not necessarily rule out the diagnosis of botulism, particularly in the event of inhaled botulism neurotoxin.
- Bacterial cultures, antibody tests, and routine laboratory tests
 - Blood, stool, sputum and urine cultures are not helpful in confirming a diagnosis of inhalational botulism.
 - Patients do not generally develop an antibody response due to the subimmunogenic amount of toxin necessary to produce disease.
 - Routine laboratory tests, including chemistries and hematologic profiles are generally within normal limits unless a secondary process (*e.g.*, *nosocomial infection*) has occurred.
 - Cerebrospinal fluid tests are generally normal in botulism (CSF protein may be elevated after 1 – 2 weeks with Guillain Barre Syndrome).

B. Electrophysiologic Studies - Should be performed on clinically-involved muscles

Tensilon test - normal (differentiates botulism from myasthenia gravis)

Nerve conduction velocity - normal

Repetitive nerve stimulation at 50 Hz - facilitation of the compound muscle action potential (rates 20-50 per second)(EMG shows an incremental response to repetitive stimulation)

These studies may support the diagnosis of botulism but a normal electromyogram does not rule out disease.

VI. Handling Laboratory Specimens

Biosafety Level 2 practices, containment equipment and facilities are recommended for all activities with materials known or potentially containing toxin. Laboratory staff handling specimens from persons who might have botulism must wear surgical gloves, protective gowns, and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (a strong alkaline solution {e.g, 0.1M sodium hydroxide} for botulinum toxin or a 1:10 bleach solution for the *Clostridium* organism) for at least 15 minutes to ensure effective inactivation. If the material is suspected to contain both toxin and organisms, the spill must be sequentially treated with bleach and sodium hydroxide.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care combined with the *rapid* administration of botulinal antitoxin are the keys to successful management of botulism. With improvements in intensive care support and early administration of antitoxin, mortality rates for botulism have been approximately 6%

in recent years. Respiratory failure due to paralysis of respiratory muscles is the most serious complication as well as the most common cause of death.

- Botulinum Antitoxin - In uncontrolled studies, use of antitoxin has been associated with lower mortality rates and, if administered early after onset of symptoms, a shorter course of illness. A licensed trivalent antitoxin is available. Current recommendations are to administer ONE 10 ml vial of antitoxin per patient, intravenously in a normal saline solution over 20 minutes. Antitoxin need not be repeated since the circulating antibodies have a half-life of 5 to 8 days. Contact Santa Cruz County Health Services Agency, Disease Control (831) 454-4114 (after hours 831-471-1183) and they will assist in obtaining antitoxin from the state.
- The antitoxin is of equine origin and requires skin testing for hypersensitivity *before* administration of the antitoxin. About 9-21 % of patients will develop either acute or delayed-type sensitivity reactions. Serum sickness reactions appear to be dose-related and may be less likely with the newer dosing recommendations.

Skin testing is performed by injecting 0.1 ml of a 1:10 dilution (in sterile physiologic saline) of antitoxin intradermally in the patient's forearm with a 26 or 27 gauge needle. The injection site should be monitored and the patient observed for allergic reactions for 20 minutes.

The skin test is positive if any of the following occur:

- a. Hyperemic areola (> 0.5 cm) at the site of the injection
- b. Fever or chills
- c. Hypotension (greater than 20 mm Hg drop in blood pressure)
- d. Skin rash or generalized itching
- e. Respiratory difficulty
- f. Nausea or vomiting

- Supportive therapy - Improvements in intensive care have significantly decreased mortality rates for botulism. Monitoring of the vital capacity is crucial and intubation is usually indicated when the vital capacity falls below 12ml/kg, without waiting for a rise in PCO₂ or fall in oxygen saturation. Ventilatory support may be required for weeks to months.
- Therapy in pediatric patients and pregnant women - therapy is identical to the recommendations outlined above.
- Aminoglycoside antibiotics are contraindicated for treatment of secondary infections since they can exacerbate the neuromuscular blockade.

VIII. Isolation of Patients

Botulism has not been transmitted from human-to-human. All staff should observe Standard Precautions when caring for patients with suspected or confirmed botulism. Patients do not require isolation rooms.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed 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 will 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.

Botulism is a reportable disease in California. *All suspect cases* should be immediately reported by telephone:

- During business hours
Santa Cruz County Health Services Agency, Disease Control at **831-454-4114**
- After business hours
Santa Cruz County Communications at **831-471-1183**

XII. References

Allen SD, Baron EJ. Clostridium. In: Balows A, Haulser WJ, Herrman KL, Shadomy HJ, eds. *Manual of Clinical Microbiology* 5th ed. Washington, DC: American Society for Microbiology; 1991:505-521.

Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: Medical and public health management. Consensus statement of the Working Group on Civilian Biodefense. *JAMA* 1999: (in preparation)

Bleck TP. Clostridium botulinum. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone;1995:2178-2182.

Centers for Disease Control and Prevention. Botulism in the United States, 1899-1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers, Atlanta, GA. Centers for Disease Control and Prevention, 1998.

Fleming DO, Richardson JH, Tulis JJ, Vesley D, eds. *Laboratory Safety Principles and Practices*. 2nd ed. Washington, DC: American Society for Microbiology;1995:324.

Holzer E. Botulism Caused by Inhalation. *Med. Klinik*. 1962;No. 41:1735-1740.

Shapiro RL, Hatheway C, Swerdlow DL. Botulism in the United States: A clinical and epidemiologic review. *Ann Intern Med* 1998;129:221-228.

Shapiro RL, Hatheway C, Becher J, Swerdlow DL. Botulism surveillance and emergency response: a public health strategy for a global challenge. *JAMA*. 1997;278:433-435.

November 2000

Used with permission and adapted from the New York City Department of Health/Bureau of Communicable Diseases