Botulism
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Botulism is the disease caused by intoxication with the botulinum neurotoxin produced by *Clostridium botulinum*.

Botulinum toxin is the most lethal substance known, with less than 1 microgram sufficient to cause fatal human disease. This toxin already has a history of use or attempted use as a biological weapon. The Japanese experimented with it in Manchuria during World War II, and it was produced by the former U.S. and Soviet Union bioweapons programs. After the Persian Gulf War, it was confirmed that Iraq had produced enough concentrated botulinum toxin to kill the entire global population and that dozens of missiles and bombs had been armed with it. In the early 1990's a Japanese cult unsuccessfully attempted to disperse botulinum toxin in Tokyo. Because of its potency, its history of use as a biological weapon, and its potential for aerosolization or food contamination, it is one of the most likely agents expected to be encountered in a bioterrorist attack. Contamination of municipal water supplies is unlikely because standard purification processes inactivate the toxin.

Naturally-occurring botulism is a rare disease with an annual incidence of approximately 100 cases in the U.S., one fourth of which are associated with foodborne outbreaks. Botulism is the result of exposure to and uptake into the body of botulinum toxin, produced by the bacterium *Clostridium botulinum*, which is found in soil throughout the world. The disease is not an infection, but an intoxication, and cannot be transmitted from person-to-person. There are three main mechanism of botulinum toxin entry into the body. The classic route of entry, leading to foodborne botulism outbreaks, is from the ingestion of preformed botulinum toxin in contaminated, often improperly prepared canned foods that contained *C. botulinum* spores. Intoxication also rarely occurs when *C. botulinum* spores germinate in a wound, typically from injection drug use, with subsequent toxin production. The majority of reported cases in the U.S. are infant botulism, which occurs sporadically as a consequence of *C. botulinum* colonization of the intestinal tract with subsequent absorption of toxin without actual infection. Rarely, this intestinal form can occur in adults. A fourth method of delivery is inhalational. Animal studies and rarely reported cases of laboratory accidents confirm that this is an efficient mechanism of delivery that quickly leads to intoxication. This is the most likely route of infection to be encountered in a large scale bioterrorism event, however foodborne botulism is a likely candidate for smaller scale events with a primary goal of spreading fear. Overall mortality for U.S. cases is less than 10%, and is rare when diagnosis is promptly made and mechanical ventilation is available. For these reasons, index cases of foodborne outbreaks have a higher mortality, and subsequent cases are more likely to receive timely antitoxin.

Clostridium botulinum is a large Gram positive spore-forming strictly anaerobic bacterium. It rarely infects humans, but it produces one of seven closely related neurotoxins, depending on the strain. These toxins are designated Type A through G. Types A, E and B are the most frequently encountered in the U.S., thus outbreaks with other types should raise greater suspicion for a possible bioterrorism-related event. All toxin types have the same general mechanism of action causing the same syndrome, but differ slightly in their structure and proteolytic activity.

This slide nicely illustrates the pathogenesis of botulism. The toxin is taken up by skeletal muscle motor neurons where it irreversibly inhibits the release of acetylcholine, resulting in post-synaptic muscle paralysis. The paralysis persists until axonal branches regenerate.

Regardless of the route of intoxication the same neurologic syndrome develops. After an incubation period of 12-72 hours, the classic syndrome appears. This is a flaccid paralysis that starts with acute symmetric cranial nerve palsies manifested by visual changes, ptosis and dysphasia, followed by descending complete skeletal muscle paralysis, including the diaphragm, leading to respiratory failure. Autonomic nervous system disturbances can include urinary retention and orthostasis. The symmetric, descending nature of the syndrome with a lack of fever and a normal mental status help to differentiate botulism from other neurological diseases.

The limited differential diagnosis for botulism includes myasthenia gravis, which would have a sustained response to anticholinesterases; Guillaine-Barre syndrome, which would involve an ascending paralysis with paresthesias and areflexia; stroke, which would likely be asymmetric and have associated abnormalities on brain imaging; tick paralysis, which would develop ascending paralysis and paresthesias with the presence of a tick; and poliomyelitis, which would be asymmetric and follow a preceding viral illness. In addition to the neurologic syndrome, there are often other features present depending on the route of intoxication. Foodborne illness is usually associated with nausea, diarrhea and dry mouth; infant botulism is often accompanied by constipation; and wound botulism would result from visible wounds.

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 clinical presentation. Laboratory confirmation can be achieved in most cases by detection of toxin in serum or stool via a mouse bioassay that is available at reference laboratories. Anaerobic culture of stool is sometimes positive for *C. botulinum*. These tests require days to complete. The rapid detection of toxin by ELISA* may be available at some reference labs.

** Editor's Note*
Transcript reflects updated/corrected information.

Because botulinum toxin inhibits acetylcholine release irreversibly, the paralysis can last for weeks to months before axonal branches regenerate. Therapy is primarily supportive, with all severe cases requiring prolonged ventilatory and nutritional support. Complications related to ventilation are the primary cause of death, thus prevention of secondary infections, such as aspiration pneumonia, is critical. If antibiotics become necessary, aminoglycosides and clindamycin should be avoided because of their neuromuscular blockade activity. Passive immunization with antitoxin is the other mainstay of management, which has been shown to decrease mortality. Antitoxin contains antibodies that bind and inactivate circulating toxin, effectively halting the progression of paralysis, but it does not reverse paralysis that has already occurred. Thus, the antitoxin must be administered as quickly as possible upon suspicion of disease, without waiting for confirmation. There are two types of antitoxin available. The first is a licensed trivalent horse serum derived antitoxin containing antibodies to the main toxin Types A, B and E. It is available from the CDC through local health departments, and causes significant hypersensitivity reactions in up to 10%, including anaphylaxis in 2%. In the event of a known release of a different toxin type, an investigational heptavalent antitoxin versus all known toxin types is available from the Department of Defense. There is less experience with this agent, but it appears to have fewer hypersensitivity reactions.

Because of the limited supplies and high risk of hypersensitivity with botulinum antitoxins, routine administration after suspected exposure is currently not recommended in asymptomatic individuals, despite animal data to suggest that this is an effective prophylactic measure. In the event of suspected exposure to aerosolized botulinum toxin, asymptomatic persons should be under close observation for at least 72 hours after suspected exposure, and antitoxin given immediately upon development of any symptoms.

Immunization with a pentavalent botulism toxoid versus Types A-E is effective at preventing botulism if given long before exposure, but has no role in post-exposure prophylaxis because it takes months to develop immunity. It is used to immunize laboratory workers and has not been tested versus inhalational exposure.

Because there is no person-to-person transmission of botulism, patients and clinical specimens can be handled following standard precautions.