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BICHAT GUIDELINES* FOR THE CLINICAL MANAGEMENT OF BOTULISM AND BIOTERRORISM-RELATED BOTULISM

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Botulism is a rare but serious paralytic illness caused by botulinum toxin, which is produced by the *Clostridium botulinum*. This toxin is the most poisonous substance known. It 100 000 times more toxic than sarin gas. Eating or breathing this toxin causes illness in humans. Four distinct clinical forms are described: foodborne, wound, infant and intestinal botulism. The fifth form, inhalational botulism, is caused by aerosolised botulinum toxin that could be used as a biological weapon. A deliberate release may also involve contamination of food or water supplies with toxin or *C. botulinum* bacteria. By inhalation, the dose that would kill 50% of exposed persons (LD50) is 0.003 µg/kg of body weight.
Patients with respiratory failure must be admitted to an intensive care unit and require long-term mechanical ventilation. Trivalent equine antitoxins (A,B,E) must be given to patients as soon as possible after clinical diagnosis. Heptavalent human antitoxins (A-G) are available in certain countries.

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Introduction

Botulism is a rare but serious paralytic illness caused by botulinum toxin, which is produced by the *Clostridium botulinum* under anaerobic conditions [1,2]. This bacterium is a common spore-forming soil contaminant. Cosmetic use of botulinum toxin to reduce wrinkles on the face and neck has become a popular alternative to cosmetic surgery. Nevertheless, botulinum toxin is the most poisonous substance known. Eating or breathing this toxin causes illness in humans.
Four distinct clinical forms are described for botulism: foodborne, wound, infant and intestinal botulism. The fifth form, inhalational botulism, is caused by aerosolised botulinum toxin [3-8].

Botulism and bioterrorism

Aerosols of botulinum toxin could be used as a biological weapon [3-8]. A deliberate release may also involve contamination of food or water supplies with toxin or *C. botulinum* bacteria. Botulinum toxin is extremely lethal and easy to produce. The Aum Shinrikyo cult in Japan, attempted unsuccessfully to release an airborne form of botulinum toxin in Tokyo on three separate occasions in the early 1990s before they finally used sarin in the Tokyo [3]. It is likely that several countries have developed and stockpiled botulinum toxin weapons [3]. In 1991, it was reported that Iraq possessed warheads with botulinum toxins [3]. It has been estimated that a point-source aerosol release of botulinum toxin could incapacitate or kill 10% of the population within 500-miles downwind [3].

Microbiological characteristics

C. botulinum is a large, Gram-positive, strictly anaerobic bacillus that forms a subterminal spore. These spores can be found in soil samples and marine sediments throughout the world. Four groups of *C. botulinum* are described. Group I organisms are proteolytic in culture and produce toxin types A,

B or F; group II organisms are non-proteolytic and produce toxin types B, E or F; group III produces toxin types C or D and group IV toxins type G. These toxins are proteins of approximately 150 000 D molecular weight and induce similar effect whether inhaled or ingested.
When ingested, toxins are absorbed in the duodenum and jejunum, and enter into the blood stream, by which they reach peripheral cholinergic synapses. Botulinum toxin does not penetrate intact skin [3]. Toxins act by binding to the presynapse nerve terminal at the neuromuscular junction and at cholinergic autonomic sites. This prevents release of acetylcholine and interrupts neurotransmission [9].
Human botulism is almost always caused by toxin types A, B, E and in rare cases F. Types C and D are associated with disease in birds and mammals. Type G is not associated with any disease in humans or animals. It has been estimated that, weight for weight, these toxins are the most toxic compounds known, with an estimated toxic dose, for toxin type A, of only 0.001 µg/kg of body weight when administered intravenously, subcutaneously or intraperitoneally [10]. By inhalation, the dose that would kill 50% of exposed persons (LD50) is 0.003 µg/kg of body weight [10]. This toxin is 100 000 times more toxic than sarin gas [7].

Clinical features

The incubation period is short, depending on the type and dose of toxin: 12-72 hours (range: 2 hours-10 days) [11]. Following aerosol exposure onset of symptoms may be more rapid, possibly occurring less than one hour after exposure (TABLE I). Person-to-person transmission has never been described.
Whatever the route of contamination, illness is an acute, afebrile, symmetric, descending flaccid paralysis that begins from the head [7]. Multiple cranial nerve palsies produce diplopia, ptosis, blurred vision, enlarged or sluggishly reactive pupils, photophobia, facial weakness, dysphonia, dysphagia and dysarthria. This is followed by a symmetrical, descending skeletal muscle paralysis with hypotonia, weakness in the neck and arms, after which respiratory muscles and then distal muscles are affected [7]. There is no loss of sensation and patients are well oriented. There may also be other autonomic signs including postural hypotension, dry mouth, and cardiovascular, gastrointestinal and urinary autonomic dysfunction. Gag reflex may not be lost. Deep tendon reflexes may be present or absent. Pupils are dilated and fixed. Respiratory paralysis may require ventilatory support. If onset is

very rapid, there may be no other symptoms before sudden respiratory paralysis occurs. Nausea, vomiting and diarrhoea followed by constipation are seen in foodborne botulism. Differential diagnoses include Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome, myasthenia gravis, tick paralysis such as Lyme disease, or magnesium intoxication. Laboratory test results, including analysis of the cerebrospinal fluid (CSF), are unremarkable [3].

Food or waterborne botulism is caused by ingestion of food containing preformed toxin. A normal healthy adult can consume small numbers of spores with no ill effect. Foodborne botulism has often been caused by home-canned foods with low acid content, such as asparagus, green beans, beets or corn. More unusual sources are chopped garlic in oil, chilli peppers, tomatoes, improperly handled baked potatoes wrapped in aluminium foil, and home-canned or fermented fish [11].

Wound botulism follows infection of wounds caused by penetrating injuries [3,11]. *C. botulinum* multiplies and produces its toxin in the contaminated wound. Injecting or sniffing drugs that are contaminated by spores have also been reported as causing botulism. Fever can be present and reflects wound infection rather than botulism. *C. botulinum* infection may produce abscess formation. Wound botulism can be prevented by promptly seeking medical care for infected wounds.

Infant botulism generally occurs in infants who are under 6 months of age and results probably from the endogenous production of toxin by germinating spores of *C. botulinum* in the intestine after ingestion of contaminated food [11]. Honey, which can contain *C. botulinum* spores, has been a source for infection for children under 12 months old.

Intestinal botulism is caused by colonisation of the gastrointestinal tract by *C. botulinum* with in vivo production of toxin [11].

Inhalation botulism does not occur naturally, but may result from an accidental or a deliberate release of toxin in the form of an aerosol. Little data concerning this route of transmission are reported in humans [3,10,12]. An incident involving the accidental exposure of three humans to botulinum toxin occurred in a laboratory in Germany [12]. Clinical features are the same as those observed with the other forms.

Diagnosis

Clinical diagnosis can be problematic without a strong clinical suspicion. The first and early cases are commonly misdiagnosed. Case definitions of suspected or confirmed cases and cases due to deliberate release are reported in Tables 2 and 3.

Laboratory diagnosis relies on isolation and identification of the neurotoxins from sera or other samples (stool, gastric specimen, vomitus, and suspect food) [3]. It has been suggested that aerosolised toxin is usually not identifiable in serum or stool [7]. The aerosolised toxin may be detectable by ELISA on nasal mucous membranes or broncho-alveolar lavage for 24 hours after inhalation. The standard laboratory diagnostic test remains the mouse bioassay (injection of serum collected before administration of antitoxin). Pus from wounds, biopsy tissues (surgical debridement), and faecal and gastric specimens can also be cultured for *C. botulinum* (anaerobic cultures).

Treatment

Without supportive treatment, death often occurs from respiratory failure. Patients with respiratory failure must be admitted to an intensive care unit and require long-term mechanical ventilation (from 60 days to 7 months) [11]. Trivalent (A, B, E) equine antitoxins must be given to patients as soon as possible after clinical diagnosis by slow intravenous infusion [3,5,6,13]. Heptavalent human (A-G) antitoxins are available in certain countries [3,14]. Anaerobic antibacterial agents can be used to treat wound infection or abscesses, but these have no effect on botulinum toxin. Antibiotic treatment is not indicated for colonisation because lysis of intraluminal *C. botulinum* may increase the amount of toxin available for absorption.

Patients with botulism who survive may have asthenia and dyspnoea for years and long-term therapy may be needed to aid recovery. Muscle functions returns after 3 to 6 months as the neuromuscular junction regenerates.

In the United States (US), investigational pentavalent (A-E) botulinum toxoid vaccine is used for laboratory workers at high risk of exposure and by military personnel. Several thousand laboratory workers have been immunised over several decades in many countries. Immunity is induced slowly by this vaccine and frequent boosters are required [15]. Experimental new vaccine candidates are currently being developed in the US and in Europe [14,16,17].

In conclusion, botulism has been reported as presenting a very high threat of being used in biological warfare. Production of the toxin has been reported in several countries, but use has never been proven.

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* **BICHAT**, the European Commission's Task Force on Biological and Chemical Agent Threats, has developed this set of guidelines that may be the basis of national authorities' guidance, and may also be used directly by clinicians, general practitioners and specialists when confronted with patients infected by agents that may be due to deliberate release of biological agents. Ref. Bossi P, Van Loock F, Tegnell A, Gouvras G. Bichat clinical guidelines for bioterrorist agents. *Euro Surveill*. 2004; 9(12)

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Editorial note: *These clinical guidelines were reviewed by the Task Force and by two experts designated by each Member State of the European Union. This review was completed at the end of February 2003. The revised guidelines were submitted to the Health Security Committee which approved them in April 2003 and agreed their publication in a widely disseminated journal so as to allow access to as large an audience as possible. The editorial process of Eurosurveillance also introduced modifications that improved the contents of these guidelines.*

TABLE 1

Summary of clinical features and diagnosis of botulism

Clinical features
o Incubation period: 12-72 hours (Following aerosol exposure <1 hour)
o Illness is an acute, afebrile, symmetric, descending flaccid paralysis that begins from the head with diplopia, ptosis, blurred vision, enlarged or sluggishly reactive pupils, photophobia, facial weakness, dysphonia, dysphagia and dysarthria
o Symmetrical, descending skeletal muscle paralysis with hypotonia, weakness in the neck and arms, after which respiratory muscles and then extremity muscles are affected
o No loss of sensory awareness and patients are well oriented
o Other autonomic signs with postural hypotension, dry mouth, and cardiovascular, gastrointestinal and urinary autonomic dysfunction
Diagnosis
o The standard laboratory diagnostic test: the mouse bioassay
o Isolation and identification of the neurotoxins from sera or other samples (stool, gastric specimen, vomits, and suspect food)
o Aerosolised toxin is usually not identifiable in serum or stool: may be detectable by ELISA on nasal mucous membranes or bronchiolar lavage for 24 hours after inhalation
o Pus from wound, biopsy tissues, faecal and gastric specimens can also be cultured for *C. botulinum* (anaerobic cultures)
Treatment
o If respiratory failure: long-term mechanical ventilation (60 days to 7 months)
o Trivalent (A, B, E) equine antitoxins as soon as possible after clinical diagnosis
o Heptavalent human (A-G) antitoxins are available in certain countries
o Anaerobic antibacterial agents: not indicated for colonisation

TABLE 2

Case definitions of suspected and confirmed cases

Suspected case
○ Any previously healthy patient with sudden onset of afebrile, symmetric, descending, flaccid paralysis with prominent bulbar palsies (diplopia, dysarthria, dysphonia, dysphagia) and clear sensorium
Confirmed case
○ A case that clinically fits the criteria for suspected botulism + ≥1 of the laboratory criteria
Laboratory criteria for diagnosis
○ Detection of botulinum toxin from serum or other pathological specimens (stool, vomits, gastric specimen) or identification of *C. botulinum* from stool

Source: [18,19]

TABLE 3

Deliberate release
○ Clusters of >2 cases of acute flaccid paralysis with prominent bulbar palsies, especially where there are common geographic factors between cases, but no common dietary exposures or injecting drug use
○ Multiple simultaneous outbreaks with no obvious common source
○ Cases of botulism with an unusual toxin type (type C, D, F or G or toxin E not acquired from an aquatic food)