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Brief Reviews

Botulism in the 21st Century: A Scoping Review

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Botulism is a potentially deadly neuroparalytic disease that affects all age groups; it is highly challenging to diagnose due to its nonspecific symptoms. Infant botulism is the most common form of botulism in the United States, followed by foodborne and wound botulism. Since most patients require hospitalization, it is imperative that both adult and pediatric physicians recognize its symptoms. Patients with severe forms of botulism typically present early after toxin ingestion and progress rapidly. Although rare in the United States, botulism remains a public health concern since even one case may predict an outbreak. This review summarizes the typical clinical course of botulism and recommendations for diagnosis and management.

BACKGROUND

Botulism is a neuromuscular paralytic disease caused by botulinum toxin, the most poisonous bacterial toxin known. The botulinum toxin is acquired in adults through ill-prepared food, a contaminated wound, or via iatrogenic injection. Infant botulism develops from in-vivo toxin production after ingestion of botulinum spores. Adult intestinal toxemia is a rare syndrome that develops from in-vivo toxin production in adults and children >1 year of age with intestinal colonization of toxigenic clostridial species.

The inhalational form of botulism is not known to occur in nature and is the result of exposure to intentionally aerosolized toxins for bioterrorism. Patients may present with ocular disturbance and/or mild weakness, which can rapidly progress to symmetric descending flaccid paralysis requiring intubation and mechanical ventilation. Continuous pulse oximetry, spirometry, and arterial blood gas measurement can be used to monitor respiratory status closely. Prolonged hospitalization may be required in severe cases.

Early antitoxin treatment is vital to avoid severe neurologic and cardiopulmonary complications, including death. An equine-derived heptavalent botulinum antitoxin (HBAT) is available from the Centers for Disease Control and Prevention (CDC) to the public state health department. In addition, human immunoglobulin is available for infants with botulism.

METHODOLOGY

We searched for English-language published studies in PubMed, Medscape, MEDLINE (from 2002 to 2022) discovered through multiple search queries specifying for "Botulism", "Foodborne botulism", "Infant botulism", "Iatrogenic botulism", "Wound botulism", "Bioterrorism", "Botulinum toxin", and "Descending paralysis". This scoping review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist.

ETIOLOGY AND EPIDEMIOLOGY

Botulinum neurotoxin is produced by *Clostridium botulinum* or related species (*Clostridium baratii and clostridium butiricum*).[1,2] *C. botulinum* is a spore-forming, anaerobic gram-positive rod ubiquitous in the environment and present in many plants and vegetables.[2] Heat resistance allows the organism to survive in an oxygen-containing environment and produce neurotoxin in anaerobic conditions, which is particularly hazardous in home-canned foods when the cooking temperature is inadequate.[2] Botulinum spores are heat resistant, and the minimum kill time varies by product and container size. Barriers to toxin production include an aerobic environment, low temperature, alkaline pH, and high sugar content. Independent of spores, the toxin is heat labile and destroyed by temperatures above 85°C for more than 5 minutes.

C. botulinum produces eight known potent neurotoxic proteins (BoNT): types A through H.[1–3] Human disease commonly associated with types A, B, E, or rarely F. Both toxin types A and B are linked to home-prepared food; type E toxin is commonly found in fish or marine animals.[2,3] Food contaminated by A and B toxins has a foul taste, while type E toxin-contaminated food is less likely to demonstrate spoilage. In the United States, type A toxin is associated with a 60% mortality rate among symptomatic individuals and is commonly found on the West Coast; type B toxin is less toxic and is associated with a 48% mortality rate. Type E outbreaks have been observed in Alaska, the Great Lakes region, and the Pacific Northwest. Alaska native populations are at highest risk for foodborne botulism due to cultural food practices.[4] Availability of precooked, "Ready to Eat" refrigerated foods presents new public health risks; commercially available food has occasionally been impli-

cated in statewide outbreaks.[5–7] Intentionally delivered BoNT through food or water supplies is an act of bioterrorism.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATIONS

Botulism toxin does not kill cells but affects peripheral nerve endings by blocking presynaptic acetylcholine release at the neuromuscular junctions of skeletal muscles, resulting in the progressive decline of muscle function leading to flaccid paralysis.[3] The central nervous system is unharmed, and the patients' mentation and sensorium are spared, although some authors have reported cases with sensory abnormalities.[8,9] Adult foodborne botulism does not require the presence of the organism. The toxin within food is resistant to gastric acid and intestinal enzymes and is readily absorbed into the bloodstream. The disease in infants results from spores' germination in the large intestine with in vitro toxin production. Adults or children >1 year old with intestinal pathology may colonize BoNT–producing clostridia as described in infant botulism.[10,11]

Typically, patients present with diplopia, blurry vision, ptosis, dysphagia, and dysphonia due to the weakness of affected small muscles of the eye, larynx, and pharynx. Dry mouth and decreased sweat production occur from the failure of acetylcholine transmission across the autonomic system. The pupils are fixed and dilated in 50% of cases. Tendon reflexes typically are intact unless the involved muscles' weakness is profound. Descending weakness is usually symmetrical without the sensory deficit and affects first the upper and then lower extremities; progression may lead to respiratory failure and cardiac arrest. Patients should be hospitalized and carefully monitored for disease progression, especially for respiratory distress. If the patient demonstrates upper airway compromise or vital capacity is < 30% of predicted, then intubation and mechanical ventilation should be performed. With optimal management and advances in critical care, mortality decreases from ~50% to 9%.[12] Patients with severe forms of botulism typically present early after toxin ingestion and progress rapidly compared to those with milder forms. Sporadic cases of botulism may be challenging to identify. A clinical tool for assisting the early diagnosis of suspected cases is based on three criteria: afebrile state, signs, and symptoms described by Rao et al.[13]

FOODBORNE BOTULISM

The incubation period for foodborne botulism ranges from 18 hours to 36 hours. Patients may present with abdominal pain, nausea, vomiting, and diarrhea. Dry mouth and blurred or double vision develop, followed by dysarthria, dysphagia, and diminished gag reflex, and 50% of patients will have fixed and dilated pupils.[13,14] Some patients may have a sore throat without fever. Ptosis is common. Autonomic nervous system involvement results in pupillary abnormalities, constipation (paralytic ileus), dry mouth, postural hypotension, and urinary retention. Heart rate, R-R interval variation, the absence of sympathetic skin response, and low plasma norepinephrine have been described in some patients.[15] Descending, symmetric flaccid paralysis will occur as the disease progresses, and without treatment, respiratory failure will develop, leading to cardiac arrest and death. Recovery from disease is usually complete but takes weeks or months.[16]

WOUND BOTULISM

Wound botulism develops from *C. botulinum*–contaminated soil. Risk factors for wound botulism are illegal intravenous drug use (primarily black-tar heroin), compound fractures involving soil contamination, and deep puncture wounds.[17] The toxin is produced in- situ and can be absorbed through mucous membranes, skin lesions, or wounds. *C. botulinum* has been cultured from the skin lesions of heroin users and from sinus aspirates of patients with intranasal cocaine use.[18,19] The incubation period varies from 7 to 21 days.

Symptoms are indistinguishable from foodborne botulism, except gastrointestinal symptoms do not occur. Wound botulism should be considered in patients with any wound associated with descending paralysis and bulbar signs. Electro-diagnostic studies should be considered if the serum is negative for toxins and the organism is not isolated from the wound. Wound care with antitoxin administration is essential, and surgical debridement is recommended even if the wound appears benign. Antibiotics, such as penicillin or metronidazole (if penicillin allergic) should be given after antitoxin administration. Aminoglysides potentiate the toxin-paralytic effect and should be avoided. A tetanus toxoid booster is also indicated.

IATROGENIC BOTULISM

Botulinum toxin was introduced as a treatment in 1980 and has since been used for various medical applications, including neurologic, gastroenterological, urologic, and dermatologic indications.[20] Iatrogenic botulism results from injection of supra-therapeutic dose(s) of botulinum toxin. Clinical clues for diagnosis include a history of botulinum toxin injections prior to muscle weakness (focal or diffuse) and autonomic nervous system disturbances at the injection site (**Figure 1**). Toxin detection in the blood confirms the diagnosis. If negative, then single-fiber electromyography (EMG) can be utilized.[21]

INFANT BOTULISM

The most common form of botulism in the United States (**Figure 2**) was first identified in 1976 among infants 5 to 13 weeks of age and was named "floppy baby syndrome."[22] While honey is a known risk factor for infant botulism, most cases in the USA are now associated with consuming *C. botulinum* from soil or industrial dust rich with spores. The disease develops from in vivo toxin production from spore germination in the large intestine. The incubation period varies from days to weeks. Since toxin absorption is minimal in infants, the disease is less severe than adult botu-

Figure 1. Left blepharoptosis after botulinum toxin injection. The patient received an unknown dose of botulinum toxin injection for cosmetic purposes 10 days prior to admission.

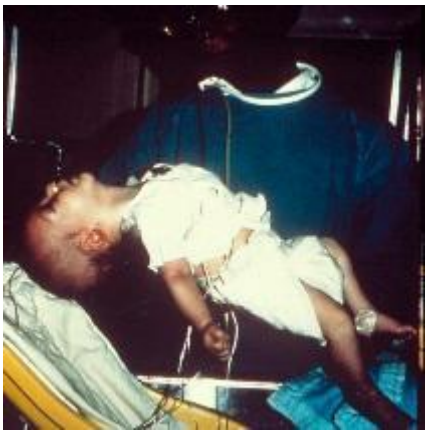

Figure 2. Infant botulism in six weeks old infant presented with marked loss of muscle tone.

Courtesy of Centers for Disease Control and Prevention image library. https://phil.cdc.gov/QuickSearch.aspx

lism; however, it may present with or progress to respiratory failure.[23] Patients usually present with constipation, weak cry, poor feeding, weak sucking reflex, failure to thrive, lethargy, and loss of strength of neck and limb muscles. The disease progresses for 1 to 2 weeks until stabilization is achieved, and about 2 to 3 weeks is required for total recovery. *C. botulinum* spores and toxins are detectable in patients' stools but not in serum samples. With supportive care, most infants recover in weeks or months without sequelae. Botulism immune globulin intravenous (human) (BIG-IV or BabyBIG®) is available for IV treatment.[23]

ADULT INTESTINAL TOXEMIA

In rare cases, adult patients can develop infant-type botulism from in vivo toxin production.[24] Patients usually suffer from various gastrointestinal tract abnormalities as observed in inflammatory bowel disease, achlorhydria, gut microflora alteration after broad-spectrum antibiotic use, or anatomical changes due to GI surgeries.[11,24] Meckel's diverticulum was identified as a risk factor for intestinal colonization by neurotoxigenic *C. butyricum*.[25] Diagnosis is based on individual clinical presentations since there are usually no links to contaminated food or wounds. However, the detection of BoNTs in serum and stools and prolonged excretion of clostridia and BoNT in the stool confirms the diagnosis.

INHALATION BOTULISM

Inhalation toxin-induced botulism cases have been reported among laboratory workers.[26,27] It may also develop from exposure to the aerosolized toxin for bioterrorism. Typical botulism symptoms develop 12 to 72 hours after inhalation. Therefore, the timely response includes early diagnosis and case reporting. Symptomatic patients should be admitted to the hospital for close observation in addition to antitoxin treatment. Decontamination includes the removal of the patient's clothing as well as showering with water and soap.

DIFFERENTIAL DIAGNOSIS OF BOTULISM

Diagnosis is based on the history and clinical presentation and must be suspected in an afebrile patient presenting with clear sensorium and descending paralysis. The presenting symptoms of botulism are nonspecific but typically begin with bulbar syndrome from cranial nerve palsies (diplopia, dysphagia, dysphonia, dysarthria). If untreated, descending symmetrical paralysis affects the trunk, extremities, and smooth muscles. Autonomic smooth muscle involvement results in constipation and urinary retention. Diaphragm weakness precipitates respiratory failure necessitating an ICU level care with intubation and mechanical intubation. The differential diagnosis for a patient who presents with descending flaccid paralytic illness includes myasthenia gravis (MG), Guillain-Barre (GB) syndrome, Miller Fisher syndrome, tick paralysis, drug side effects, stroke, toxic diphtheria, a viral illness associated with flaccid paralysis, and Lambert-Eaton myasthenia syndrome (**Table 1**).

LABORATORY TESTING

The mouse bioassay is the only currently validated laboratory diagnostic test for the diagnosis of botulism.[28] Laboratory confirmation criteria include detection of preformed BoNT in food or clinical specimens or identification of BoNT-producing clostridia in the stool; laboratory confirmation of one case in a multi-case event confirms all patients with botulism symptoms. Botulinum toxin can be detected in patients' serum with foodborne botulism for up to 16 days after admission. A wound exudate and tissue specimen should also be tested to increase the likelihood of toxin detection in wound botulism.

Table 1. Differential Diagnoses of Botulism

Disease	Diagnostic clues
Botulism	No fever. Clear mentation and sensorium. Onset with cranial nerve involvement. Symmetric, bilateral, descending flaccid paralysis. Normal CSF and brain imaging EMG: incremental pattern after fast rate repetitive nerve stimulation
Myasthenia Gravis (MG)	Pupillary reflexes spared Serum acetylcholine receptor antibodies positive EMG demonstrates discriminental pattern with repetitive muscle stimulation Edrophonium (Tensilon) test +
Familial infantile MG (infants)	Family history of maternal MG
Guillain-Barre Syndrome Miller Fisher syndrome (MFS)	Usually, ascending paralysis Deep tendon reflexes (DTR) absent Sensory abnormalities Elevated protein in CSF Ophthalmoplegia with ocular and bulbar abnormalities Serum detection of autoantibodies to GQ1b EMG demonstrates the peripheral nerve lesion
Spinal muscular atrophy (infants)	Proximal muscle weakness, hypo- or areflexia, tongue fasciculation. Molecular genetic testing for targeted mutation analysis EMG, muscle biopsy (rarely performed)
Metabolic disorder (infants)*	Appropriate Screening
Heavy metal poisoning	Blood, urine test for suspected metal measurement
Lambert-Eaton myasthenia Syndrome	Extraocular and lid levator muscles are less affected Electrodiagnostic studies: 100 % increase in muscle action potential after repetitive nerve stimulation. Serum high titers of P/Q-type voltage-gated-calcium channel antibodies
Poliomyelitis	PCR, serology
Tick paralysis	Seasonal (spring or summer). Resembles GBS. Removing a tick speeds recovery
Mushrooms intoxication	History, clinical presentation
Drug side effect**	Medication information
Toxic diphtheria associated neuropathy	PCR in nasopharyngeal swab, serum Immunology. A bulbo-facial weakness and demyelinating neuropathy develop weeks after disease onset with tonsillar exudate
Hypermagnesemia Hypocalcemia	Serum magnesium level Serum calcium level

Note: Some patients with botulism show a beneficial response to anticholinesterase drugs.
*Metabolic disorders: Leukodystrophy, Urea cycle defect, Mitochondrial disorders,
Glutaric aciduria type I, Carnitine deficiency, Leigh syndrome, Congenital disorder of glycosylation, Maple syrup urine disease, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Succinic semialdehyde dehydrogenase deficiency Urea cycle defect.
Diagnosis for infant with botulism may also include cerebral infarctions, acute disseminated encephalomyelitis, acute transverse myelitis, Chiari malformation, spinal epidural hematoma,
Nemaline myopathy.
* *chloroquine, d- penicillamine, tiopronin.

In vitro methods used for food and culture testing for clinical specimens—enzyme-linked immunoassay for detection of toxins A, B, E, and F, and botulinum toxin gene real-time PCR to detect toxin genes A through G—are available through the CDC Laboratory Response Network but are not approved by the US Food and Drug Administration. EMG testing may be utilized in patients with negative toxin essay; high-frequency nerve stimulation with increased evoked muscle potential confirms the disease. CDC accepts specimens for testing from state public health laboratories and other federal agencies. Information regarding specimen collection may be obtained at the CDC website (www.cdc.gov/botulism/botulism-specimen.html)

TREATMENT

Supportive care with nutrition and respiratory support is essential for all patients with a diagnosis or suspicion of botulism.[16,28] Equine serum heptavalent botulism antitoxin is available for IV administration. It is the only botulinum antitoxin product licensed for the treatment of non-infant botulism in the United States.[12,29] Each volume contains serotypes A, B, C, D, E, F, and G. Immediate administration of antitoxin is imperative for the prevention of paralysis since the botulinum toxin binds irreversibly to neurons. Delayed antitoxin administration is ineffective in reversing the paralysis.[30] A meta-analysis of patients with foodborne botulism from 1923 to 2016 found reduced mortality with any antitoxin treatment administered within 48 hours of illness onset but did not identify an interval

beyond which antitoxin was not beneficial.[12] Therapeutic agents such as cathartics and enemas to clear toxins from the gastrointestinal tract were not found to be effective. Antibiotics are not indicated. Aminoglycosides, magnesium salts, cyclosporine, penicillamine, and quinine can potentiate neuromuscular block and should be avoided. A review of the safety of HBAT demonstrated that <1% of recipients experienced an HBAT-related serious adverse event, 9% of patients had non-serious adverse events (fever, rash), and anaphylaxis incidence was <2%. Resources needed for skin testing, benefits of early treatment, and fatal outcomes do not support performing skin tests and delaying HBAT.[20,31]

CARE OF HOSPITALIZED PATIENTS

Clinicians treating a person who has been exposed to botulism toxin or who demonstrates any clinical signs or symptoms of botulism should immediately contact their local and state health departments. CDC's Botulism Clinical Consultation Service or the state health department epidemiologist (in California and Alaska) are available for an immediate consultation. When indicated, CDC will urgently dispatch HBAT from federal stockpiles. The state health department will facilitate the collection of specimens and testing at a public health laboratory. The Botulism Treatment and Prevention Program of the California Department of Health Services should be contacted for BABY-BIG or BIG-IV release for infant botulism, regardless of the state of residency. Children with clinical evidence of botulism should be treated rapidly, given that death can occur early in the disease course, and children who receive antitoxin have better survival.[31]

A recent systematic review of 360 pediatric botulism cases treated with antitoxin worldwide revealed that those who received antitoxin had better survival.[31] Overall mortality was 23%; intensive care admission was required in 14% of cases, and mechanical ventilation in 25%. Dysphagia (53%), dysarthria (39%), and generalized weakness (37%) were the most frequently reported signs and symptoms. Pregnant patients may be at increased risk for respiratory failure; in addition to close monitoring and timely treatment with botulinum antitoxin, admission to the intensive care unit should be considered. No data support that pregnancy or postpartum state increases susceptibility to botulism.[32] Botulism does not transmit person-to-person, and no precautions beyond standard precautions are indicated. Patients do not develop natural immunity after an acute illness.

PREVENTION

Prevention of foodborne botulism includes careful practices with home food preparation. A general guideline is to boil (100 °C) home canned foods for at least 10 minutes before eating, mainly if there is a risk that they were initially under-processed. Honey consumption is contraindicated in infants. Upon exposure, a botulinum toxoid vaccine is available for laboratory workers and military personnel.

DISCLOSURES/CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

All Authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the ICJME criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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