

Clinical Considerations

Initial presentation and evaluation

Because preliminary laboratory testing results for botulinum toxin takes 5 to 7 days, the initial diagnosis depends on accurate and rapid clinical assessment. A careful history often reveals recent consumption of traditional Alaska Native foods, particularly aged foods. The incubation period, or interval from consumption of contaminated food to illness onset is typically between 12 to 48 hours. Longer incubation periods out to 84 hours have been recorded for some patients who reported vague symptoms and did not have laboratory-confirmed specimens, but were counted as cases given their exposure to toxin-containing food products. Severely affected patients may have a more rapid onset (as short as 6 hours) and although unusual, incubation periods as long as 10 days have been described.

Table 7. Signs and symptoms of botulism.

System	Sign/symptom
Gastrointestinal / Urinary	<ul style="list-style-type: none">• Abdominal pain• Diarrhea• Intestinal ileus• Nausea• Urinary retention• Vomiting
Neurologic	<ul style="list-style-type: none">• Blurry vision• Decreased gag reflex• Dilated or unreactive pupils• Diplopia• Dry mouth• Dysphagia
Muscular	<ul style="list-style-type: none">• Dyspnea (without typical signs, such as gasping)• Fatigue• Respiratory muscle paralysis• Symmetrical skeletal muscle weakness

Botulinum toxin acts at cholinergic neuromuscular junctions by blocking the release of acetylcholine. The action only affects peripheral sites and is believed to be irreversible. Both autonomic and voluntary motor activities are affected and molecular differences in toxin types may result in different

signs and symptoms. The salient clinical features of botulism can be grouped into three major areas: gastrointestinal/urinary, neurologic, and muscular (Table 7). A detailed list of possible symptoms can be found on the botulism case report form (available with other botulism resources at: <http://www.epi.alaska.gov/id/botulism/resources.htm>).

a. Gastrointestinal / Urinary

Gastrointestinal symptoms are usually the initial manifestations of botulism; however, they lack diagnostic specificity unless associated with other findings. Nausea, vomiting, diarrhea, and abdominal pain may be present initially or appear within 2-3 days of illness onset. The origin of these symptoms is not completely clear, but may be secondary to toxin-induced intestinal ileus. Ileus is sometimes severe and relatively long-lasting (i.e., more than a week). Aged foods might also contain additional bacteria or substances that could cause acute onset of vomiting and diarrhea within hours of consumption, and which may resolve quickly. A diagnosis of botulism is sometimes ruled out in these patients; however, it is important to consider the possibility that two disease processes are occurring from the same meal. Urinary retention, presumably caused by detrusor weakness, is often present; however, early in the course of the illness, it is frequently asymptomatic.

b. Neurologic

When the effects of the cholinergic blockade are observed, the diagnosis of botulism must be seriously considered, especially in an Alaska Native patient with gastrointestinal symptoms. Dryness of oral mucous membranes may be extreme and can lead to fissuring of the tongue and severe pharyngeal pain. In the past, the pharyngeal presentation of botulism was confused with diphtheria. Ocular findings are classic: diplopia, blurry vision, and fixed or dilated pupils. Ptosis is commonly present. The absence of ocular findings does not rule out the diagnosis of botulism. However, the absence of any objective signs of cranial nerve deficits makes botulism extremely unlikely; typical deficits are listed in Table 8. The progressive paralysis typically descends, affecting the cranial nerves first, then the neck, upper arms, trunk, and diaphragm, and finally the hands and legs. The fingers may be affected last.

Neurologic findings are typically bilateral. Although asymmetry of certain deficits may occur, truly unilateral deficits are uncommon. Botulism can also markedly impair control of

heart rate and blood pressure, and cause bradycardia and hypotension.³⁵

Table 8. Typical manifestations of cranial nerve deficits resulting from botulism.*

Cranial Nerve	Finding with Botulism
III – Oculomotor	Can't move eyes left and right, eyelids droop (ptosis)
IV – Trochlear	Can't look downward symmetrically
V – Trigeminal	Can't bite down
VI – Abducens	Can't look outward
VII – Facial	Can't close eyes against force, purse lips or smile
X – Vagus	Diminished gag reflex and difficulty swallowing, saying "Ah"
XI – Accessory	Diminished strength trapezius and sternocleidomastoid
XII – Hypoglossal	Difficulty moving tongue side to side

*Adapted from Table 4.¹¹

c. Muscular

Skeletal muscle weakness, manifested by fatigue, shoulder, neck or truncal weakness, or dyspnea, is an ominous sign. Because the muscles of respiration are weakened, typical signs of dyspnea such as gasping, vigorous chest motions or use of accessory muscles of respiration are usually absent. Precipitous deterioration of respiratory reserve with concomitant respiratory arrest has caused almost all of the early deaths from botulism and is not necessarily preceded by other complaints. Often a patient's paralysis prevents demonstration of agitation or restlessness, so he or she may appear to be resting comfortably. It is imperative that respiratory reserve be assessed and followed diligently. Measurement of forced vital capacity (FVC) should be sufficient to indicate the degree of respiratory compromise and is a convenient index to follow for signs of deterioration.

Assessing changes to FVC via spirometry or other formal pulmonary function testing is an objective method of documenting diminishing respiratory capacity and muscular weakness. Other quick and more subjective tests can also provide evidence of muscular impairment. For example, serial counts of how many times a patient can successively stand up and sit down, or the number of stairs they can walk up and down before becoming fatigued can provide evidence of progression of muscular weakness. This information can be used together with other signs and symptoms to support a clinical diagnosis of botulism.

Knowledge of findings that should be normal in botulism may be helpful in establishing or ruling out the diagnosis. Body temperature, orientation to person, place and time, sensory examination, and deep tendon reflexes (if the patient is not completely paralyzed) should all be normal. Rare exceptions have occurred. Even if signs or symptoms not usually associated with botulism are present, clinicians may still need to consider botulism in the differential diagnosis, especially if other findings are suggestive.

The differential diagnosis of botulism (Table 9) generally involves consideration of rare conditions or unusual presentations of common problems, such as stroke. It is often best to pursue a diagnosis of botulism, perhaps in parallel with others, until the diagnosis is clear, particularly if the patient is an Alaska Native who has consumed traditional foods during the week before onset of symptoms.

Laboratory data from electromyography, nerve conduction studies, cerebrospinal fluid analysis, or Tensilon® testing are more helpful for diagnosing other conditions than for establishing the diagnosis of botulism. Occasionally an electromyogram will show convincing post-tetanic potentiation, which is almost specific for botulism. Cerebrospinal fluid and nerve conduction studies should be normal in patients with botulism.

Past reports have suggested that if a patient has three or more signs or symptoms in a "diagnostic pentad" (Table 10) and a history of consuming traditional Alaska Native food, botulism should be strongly suspected.^{26,36} The term "diagnostic pentad," however, can be misleading because when pentad symptoms are present, they are *suggestive*, but not necessarily diagnostic, of botulism.

Table 9. Differential diagnosis for botulism.

Condition	Points of Differentiation from Botulism
Diphtheria*	<ul style="list-style-type: none"> • Cardiac conduction abnormalities • Cervical adenopathy • Culture • Fever • Typical pharyngeal or nasal mucosal lesions
Drug ingestion/ Poisoning	<ul style="list-style-type: none"> • Central nervous system abnormalities • Drug levels • History
Gastroenteritis	<ul style="list-style-type: none"> • Lack of autonomic, ocular or muscular findings
Guillain-Barré syndrome	<ul style="list-style-type: none"> • Abnormal nerve conduction • Absent deep tendon reflexes • Cerebrospinal fluid protein elevated • Sensory findings
Myasthenia gravis	<ul style="list-style-type: none"> • Response to Tensilon® testing
Paralytic shellfish Poisoning*	<ul style="list-style-type: none"> • History
Poliomyelitis*	<ul style="list-style-type: none"> • Abnormal cerebrospinal fluid • Muscle denervation findings • Presence of sensory findings
Stroke	<ul style="list-style-type: none"> • Absence of gastrointestinal and autonomic findings • Unilateral findings

*Note: in addition to botulism, suspected or confirmed cases of these conditions must also be reported to the Alaska Section of Epidemiology: see <http://www.epi.alaska.gov/pubs/conditions/ConditionsReportable.pdf>.

Also listed in Table 10 is a botulism “clinical paradigm” that focuses on body systems (i.e., gastrointestinal, neurologic, muscular) and may be a more useful screening tool in assessing suspected cases of botulism compared with the pentad. Similarly, the pentad may be more meaningful when signs or symptoms are considered with respect to body systems, e.g., dry mouth from cholinergic blockade, as opposed to resulting from repeated vomiting and subsequent dehydration.

Neither of these approaches have been rigorously tested, but both have been found useful by health care providers experienced in the diagnosis of botulism in Alaska and may help trigger suspicion of botulism. Regardless of the approach, all relevant clinical and exposure information should be considered when assessing whether a patient might have an illness compatible with a diagnosis of botulism.

Table 10. Signs and symptoms profiles suggestive of botulism.

Botulism should be considered in any patient having a history of consumption of traditional Alaska Native food with either of the following symptom profiles:

At least three of the five following signs or symptoms of a botulism “diagnostic pentad”:

- Dilated or fixed pupils
- Diplopia
- Dry throat
- Dysphagia
- Nausea or vomiting

Any of the following elements of a botulism clinical paradigm:

- Gastrointestinal symptoms with autonomic or neurologic abnormality*
- Cranial nerve deficit with no apparent cause**
- Descending symmetrical paralysis or weakness with no apparent cause

*Autonomic involvement includes evidence of hypotension.

**See Table 8, page 13.

Hospital course and treatment

Clinical caution: Most information regarding clinical course and treatment has been based on the experience of health care providers in Alaska treating Alaska Natives with botulism acquired from consumption of aged traditional foods. Providers should be aware that the clinical course and recovery may be quite different for persons with botulism acquired from consumption of home-canned products. The clinical courses for infant, wound or botulism possibly as a result of a bioterrorism attack, may also be quite different. The clinical course and appropriate management of any botulism patient needs to be tailored to current circumstances. Providers with experience in Alaska or medical toxicologists may be useful resources in managing individual patients with any kind of botulism.

The most urgent clinical concern for the patient suspected of having botulism is assessment of respiratory reserve. Most patients will require frequent (at least hourly initially) determination of FVC or an equivalent measure. Any significant decline in respiratory function should prompt consideration of endotracheal intubation and assisted ventilation. For patients in an outlying hospital requiring transfer for management of respiratory insufficiency, placement of endotracheal and nasogastric tubes should be strongly considered *before* transfer.

Convalescence after foodborne botulism can be prolonged. Few data are available on long-term sequelae among botulism survivors.

Antitoxin use and clinical management

Although the primary treatment for botulism patients is supportive care, antitoxin is available from the U.S. Centers for Disease Control and Prevention (CDC) and is indicated for persons suspected of having botulism intoxication. Before 1999, an equine trivalent antitoxin was used. From 1999-2010, botulinum antitoxin was available in two formulations: bivalent type A/B, and type E. Antitoxin type E was considered an Investigational New Drug which meant that specific guidelines and protocols had to be followed during and after administration.

In March 2010, CDC began to supply the Alaska Section of Epidemiology with a new heptavalent botulinum antitoxin

(HBAT) produced by Cangene Corporation to replace the types A/B and E antitoxin products.³⁷ HBAT contains antibodies specific for seven toxin types (A–G) and is also an Investigational New Drug.

Antitoxin kits are packaged by the Alaska Section of Epidemiology and supplied to certain hospital pharmacies located throughout the state. The Section of Epidemiology has additional kits stocked in Anchorage to be sent as needed to other locations.

In Alaska, serum sickness and anaphylaxis, although reported elsewhere, have not been documented following administration of antitoxin. Before 1999, there was only one documented case of a hypersensitivity reaction following administration of antitoxin in Alaska. No adverse reactions were reported from 1999-2010 when bivalent type A/B, and type E antitoxin formulations were administered. As well, no adverse reactions have been reported to date from the use of HBAT.

In the past, prior to any antitoxin administration, sensitivity testing was recommended. Before 1999, this may have involved instillation of product in patients' eyes. From 1999-2010, the recommended testing procedure was via a skin scratch/prick test. With HBAT, sensitivity testing prior to administration is no longer recommended.

Detailed administration information is available in the HBAT kits and should be followed closely. Section of Epidemiology staff are available 24 hours a day for assistance in interpreting instructions.

A recent review of laboratory-confirmed Alaska cases demonstrated that toxin could be found in patients' sera up to 11 days after ingestion, suggesting that HBAT could still be of clinical value to these patients.³⁸

Botulism antitoxin acts by blocking the attachment of circulating toxin to presynaptic acetylcholine release sites. At sites where toxin has already bound, antitoxin will not "neutralize" or reverse the effect of bound toxin. The effects of toxin resolve only as presynaptic end plates regenerate with time. Patients who receive antitoxin should not be expected to have immediate reversal or improvement of clinical signs and symptoms. Approximately one third of patients in one case series had continuing neurologic and muscular deterioration after receiving antitoxin.³⁹ Close observation of all patients must be maintained after treatment.

Because antitoxin can stall the toxin binding process, health care providers should administer antitoxin immediately upon the suspected diagnosis in all but the mildest cases of foodborne botulism.

Descriptions of foodborne botulism often emphasize the long duration of toxin effect.⁴⁰ However, Alaska Natives with botulism have had a remarkably more benign course, generally with rapid and complete recovery.³⁹ Most patients requiring intubation and mechanical ventilation can be successfully extubated within days. Tracheostomy should be considered rarely as the duration of respiratory paralysis is usually short. Even so, each patient's respiratory capacity must be individually assessed. For example, in 2001, one patient, with a history of underlying respiratory dysfunction, required over 3 weeks of mechanical ventilation, and subsequently had a tracheostomy.

Patients with moderate to severe symptoms are prone to develop intestinal ileus and urinary retention. Ileus is of concern because retained gastric secretions may be aspirated and decreased intestinal motility may allow continued absorption of toxin. Nasogastric tube drainage is often useful to decompress the stomach. If bowel sounds are present and the suspect meal was eaten within the last 24 hours, administration of activated charcoal with a cathartic may decrease further absorption of the toxin from the gastrointestinal tract. However if decreased motility is suspected, the patient should not receive charcoal as an ileus may lead to bowel obstruction, abdominal distention that complicates ventilation, or vomiting and aspiration. Urinary retention is also a concern and, if present, is best managed by catheterization. A bedside bladder scan may help identify early urinary retention in patients with mild paresis.

Nosocomial infections may complicate the recovery of severely affected patients; fever is the cardinal sign of secondary infection because botulinum toxin itself does not provoke fever. Pneumonia is the most frequent complication and appears to be due to a variety of factors including reduced gag reflex, highly inspissated respiratory secretions, atelectasis associated with low tidal volumes, and aspiration of pharyngeal or gastric secretions due to paralysis or weakness. Protection of the airway, high environmental humidity, adequate lung expansion, and use of mucolytic agents may all help to reduce pulmonary infection. Urinary tract infections have been reported but may be related to catheter use. Bed

sores and secondary skin infection may occur if a paralyzed and intubated patient is not turned frequently and inspected for early skin breakdown.

Recovery

It is important for health care providers of a completely paralyzed patient to remember that the person is fully awake. The illness, procedures, and medical routines should be explained with recognition that the patient is conscious. Health care providers should provide appropriate pain control and sedation for intubated patients who are otherwise alert. Patients can have excellent recall for events and conversations heard during total paralysis.

Alaska patients generally have rapid recovery of respiratory function, but may have lingering ocular or intestinal symptoms. Persistent ileus has delayed oral feeding in some patients for several weeks and necessitated total parenteral nutrition. The risk of aspiration of gastric contents exists until the gag reflex has clearly returned and ileus resolved. If any concern about swallowing ability is present, it is reasonable to conduct either a swallowing evaluation, similar to those used in stroke assessment, or a radiologic evaluation of swallowing prior to beginning oral feeding. Complete resolution of all effects of botulinum toxin is expected for most botulism patients within 1 or 2 months.

There is no evidence to suggest that having a history of botulism intoxication mitigates the course of a subsequent illness; several previous botulism patients in Alaska have experienced another episode of botulism following consumption of traditional Alaska Native foods.⁴¹ This has also been documented in Canada.⁴² Based on evidence from a survey of botulism knowledge among Alaska Natives, almost half the respondents believed that there was some form of immunity to botulism.²⁷ Health care providers should ensure that current patients are aware they may contract botulism in the future if they are exposed again and should educate them about how to avoid contracting botulism.