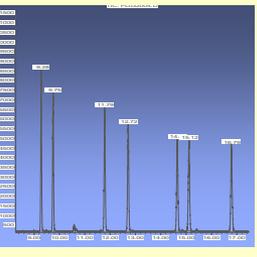
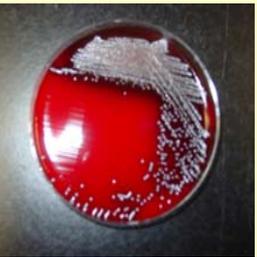




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Botulism: Clinical Aspects

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Michigan Department of
Community Health

Botulism – Michigan

The largest outbreak of botulism reported in the United States is under investigation by local, state, and federal health officials in Michigan.

On March 31, 1977, the Michigan State Department of Public Health learned that 2 employees of a hospital in Pontiac, Michigan, had been admitted to the hospital with signs and symptoms compatible with botulism. Both individuals had in common a food exposure at a Mexican restaurant located near the hospital in Pontiac. By the next

probable cases had been identified. Ten persons eaten at the implicated restaurant on the only food item eaten by all of the persons was prepared with red tomato sauce and jalapeño peppers.

Persons who used fresh peppers and had only eaten jalapeño peppers on March 28. A sample of the peppers and stools from ill persons were found to contain type B botulinum toxin. By April 1, all clinical signs compatible with botulism had disappeared among the several hundred persons

who had eaten at the restaurant. No deaths had occurred. Most of the patients were residents of Michigan, but 1 was a visitor from Ohio who became ill after leaving Michigan.

All patients with clinical findings consistent with botulism were treated with trivalent (ABE) antitoxin. County officials closed the restaurant on March 31.

Reported by L Glass, MD, Bloomfield Hills; R Locey, MD, A Markowitz, MD, Oakland County Health Dept, Michigan; the staff of the following hospitals: St. Joseph Mercy Hospital, Pontiac; Crittenton Hospital, Rochester; William Beaumont Hospital, Royal Oak; Little Traverse Hospital, Petoskey; and St. Lawrence Hospital, Lansing, Michigan; and Medical College of Ohio Hospital, Toledo, Ohio; NS Hayner, MD, State Epidemiologist, Michigan State Dept of Public Health; TJ Halpin, MD, State Epidemiologist, Ohio State Dept of Health; Food and Drug Administration; Enterobacteriology Br, Bacteriology Div, Bur of Laboratories, Field Services Div, and Enteric Diseases Br, Bacterial Diseases Div, Bur of Epidemiology, CDC.

Editorial Note: The largest previous outbreak of botulism occurred in 1921 in Michigan and affected 29 persons, 3 of whom died. That outbreak of type A botulism was caused by commercially canned spinach.

THE MIRACLE AT PONTIAC

*The Terrifying Hour-by-Hour Account
Of How Medical Detectives Cheated Death
In the Nation's Worst Botulism Outbreak*

It Began Here



The Plate of Poison



Nachos — peppers and cheese on corn chips.

The Sunday News Magazine,
May 22, 1977

CDC MMWR April 22, 1977



Jars of contaminated Jalapeño peppers involved in an outbreak of botulism in Pontiac, Michigan, April, 1977. (CDC-PHIL)

Botulism- Clinical Syndromes

I. Ingestion of toxin

- Wound
 - Contamination of wounds by soil
 - Improper fracture management
 - Black-tar heroin “skin-popping”
 - Cocaine- sinusitis
- Intentional (terrorism)
 - Inhalational
 - Foodborne
 - waterborne
- Inhalational
 - Laboratory workers
- Foodborne
- Waterborne*
- Post-therapeutic/cosmetic

*unlikely with water treatment processes



Botulism- Clinical Syndromes

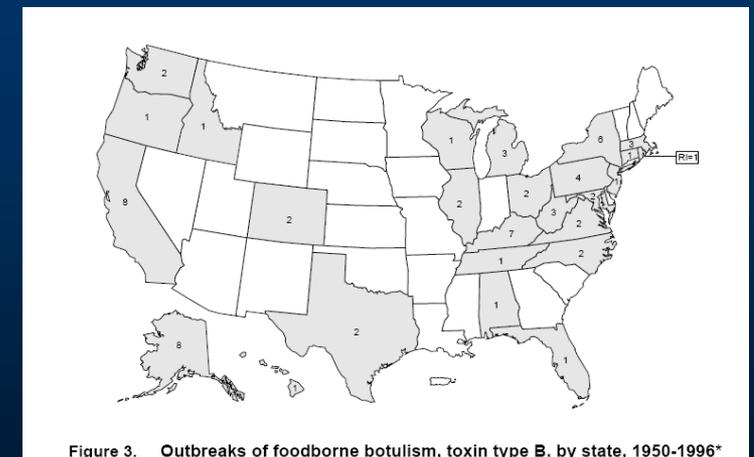
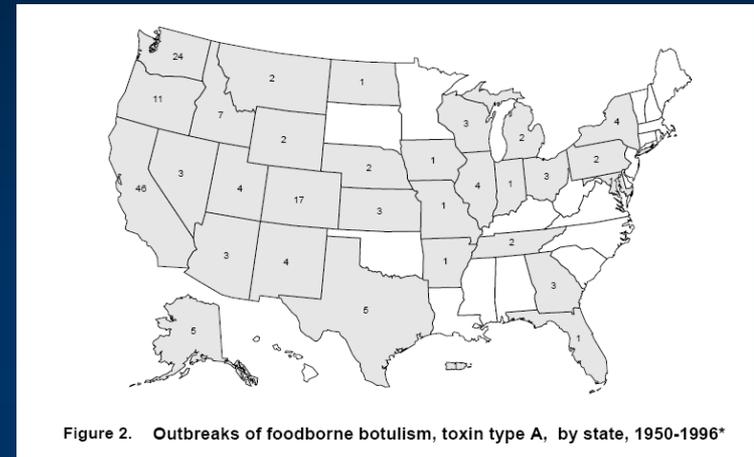
II. Ingestion of spores

- Infant botulism
 - Ingestion of food (raw honey)
 - Ingestion of soils
- Adult (intestinal) botulism
 - Prior antimicrobial use
 - Altered anatomy
- Spores germinate in colon



Epidemiology

- Frequency: <200/yr US
- Incubation: 6h-10 days
 - Foodborne- 12-36 hours to several days
 - Shorter incubation-> higher case fatality
 - Infant/adult intestinal-variable
 - Inhalational- 12-80 hours
- Transmissibility: None known

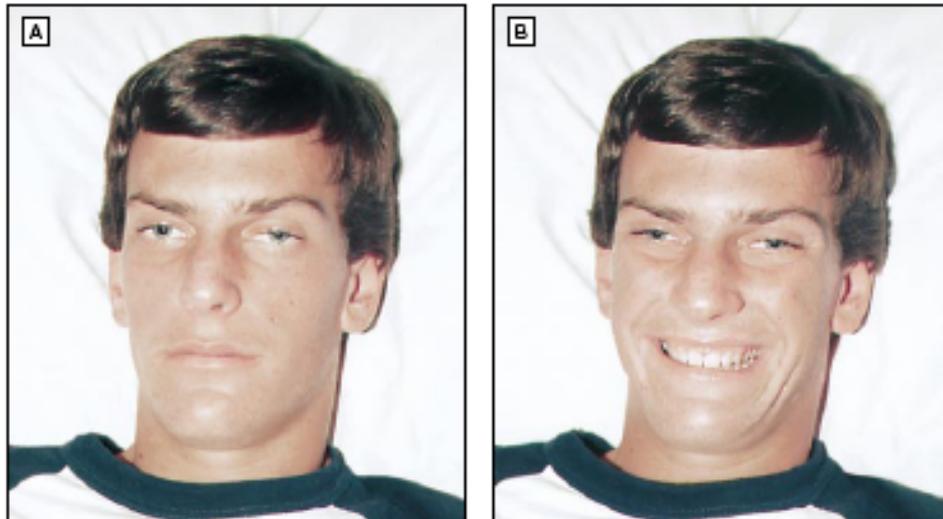


Centers for Disease Control and Prevention. 1998. Botulism in the United States, 1899 – 1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers.



Botulism Symptoms

Figure 2. Seventeen-Year-Old Patient With Mild Botulism



A, Patient at rest. Note bilateral mild ptosis, dilated pupils, disconjugate gaze, and symmetric facial muscles. B, Patient was requested to perform his maximum smile. Note absent periorbital smile creases, ptosis, disconjugate gaze, dilated pupils, and minimally asymmetric smile. As an indication of the extreme potency of botulinum toxin, the patient had 40×10^{-12} g/mL of type A botulinum toxin in his serum (ie, 1.25 mouse units/mL) when these photographs were taken.

Table 1. Symptoms and Signs of Foodborne Botulism, Types A and B*

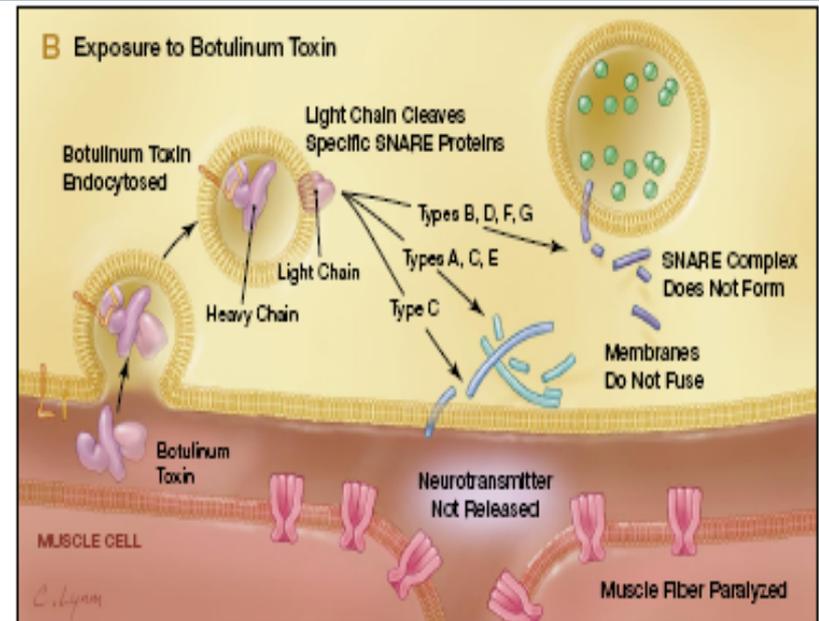
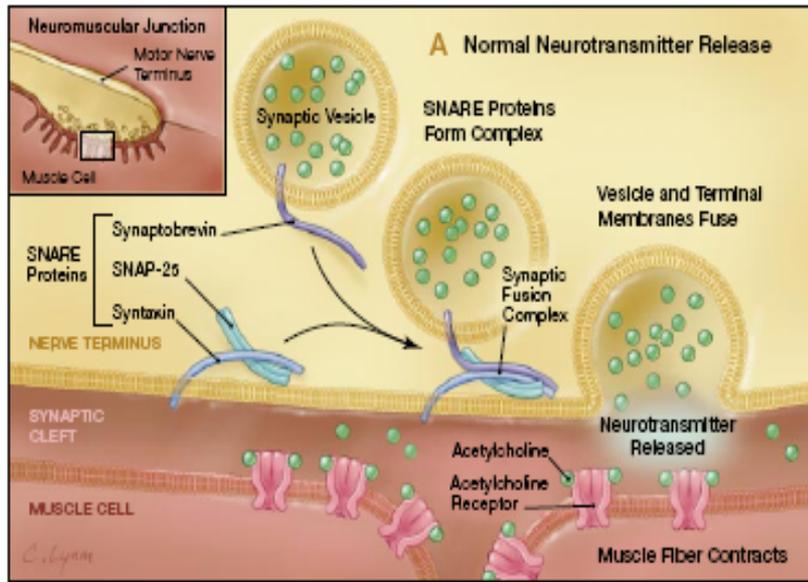
	Cases, %
Symptoms	
Fatigue	77
Dizziness	51
Double vision	91
Blurred vision	65
Dysphagia	96
Dry mouth	93
Dysarthria	84
Sore throat	54
Dyspnea	60
Constipation	73
Nausea	64
Vomiting	59
Abdominal cramps	42
Diarrhea	19
Arm weakness	73
Leg weakness	69
Paresthesia	14
Signs	
Alert mental status	90
Ptosis	73
Gaze paralysis	65
Pupils dilated or fixed	44
Nystagmus	22
Facial palsy	63
Diminished gag reflex	65
Tongue weakness	58
Arm weakness	75
Leg weakness	69
Hyporeflexia or areflexia	40
Ataxia	17

*Data are from outbreaks of botulism reported in the United States in 1973-1974. The number of patients with available data varied from 35 to 55. Adapted from Hughes et al¹⁸ with permission.

Arnon SS et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 2001; 285:1059-1070.

Mechanism of Botulism Toxin

Figure 1. Mechanism of Action of Botulinum Toxin



A, Release of acetylcholine at the neuromuscular junction is mediated by the assembly of a synaptic fusion complex that allows the membrane of the synaptic vesicle containing acetylcholine to fuse with the neuronal cell membrane. The synaptic fusion complex is a set of SNARE proteins, which include synaptobrevin, SNAP-25, and syntaxin. After membrane fusion, acetylcholine is released into the synaptic cleft and then bound by receptors on the muscle cell.

B, Botulinum toxin binds to the neuronal cell membrane at the nerve terminus and enters the neuron by endocytosis. The light chain of botulinum toxin cleaves specific sites on the SNARE proteins, preventing complete assembly of the synaptic fusion complex and thereby blocking acetylcholine release. Botulinum toxins types B, D, F, and G cleave synaptobrevin; types A, C, and E cleave SNAP-25; and type C cleaves syntaxin. Without acetylcholine release, the muscle is unable to contract.

SNARE indicates soluble NSF-attachment protein receptor, NSF, N-ethylmaleimide-sensitive fusion protein; and SNAP-25, synaptosomal-associated protein of 25 kd.

Arnon SS et al. Botulinum toxin as a biological weapon: medical and public health management.

JAMA 2001; 285:1059-1070

Botulism Diagnosis

- Suspect in any adult with findings:
 - gastrointestinal (constipation, nausea, vomiting)
 - autonomic (e.g., dry mouth, difficulty focusing)
 - cranial nerve (diplopia, dysarthria, dysphagia)
- Suspect in any infant with:
 - poor feeding
 - diminished sucking and crying ability
 - neck and peripheral muscle weakness
 - and/or ventilatory distress.



Differential Diagnosis

- Guillain-Barre syndrome
- Myasthenia gravis
- Cerebrovascular accident (CVA)
- Bacterial and/or chemical food poisoning
- Tick paralysis
- Chemical intoxication (e.g., carbon monoxide)
- Mushroom poisoning
- Poliomyelitis
- Ingestion of marine biotoxins (eg paralytic shellfish poisoning)

Rapidly Exclude Botulism

Tests to Consider:

- Lumbar puncture
- CNS Imaging
- Tensilon test
- Tick inspection
- EMG
- Autoantibodies
- Stool culture
- Campylobacter



Arnon SS et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 2001; 285:1059-1070.

Botulism-Bioterror

- Most potent toxin known to man
- Pancho Villa- 1910
- WWII
- US and Soviet
 - Agent X
 - Aerosolization inferior to that of anthrax and tularemia
 - Relative instability
- Iraq-19,000L (UN)

Likely modes:

- Aerosol (enc. areas)
- Contamination of food

Box 1. Features of an Outbreak That Would Suggest a Deliberate Release of Botulinum Toxin

Outbreak of a large number of cases of acute flaccid paralysis with prominent bulbar palsies

Outbreak with an unusual botulinum toxin type (ie, type C, D, F, or G, or type E toxin not acquired from an aquatic food)

Outbreak with a common geographic factor among cases (eg, airport, work location) but without a common dietary exposure (ie, features suggestive of an aerosol attack)

Multiple simultaneous outbreaks with no common source

Note: A careful travel and activity history, as well as dietary history, should be taken in any suspected botulism outbreak. Patients should also be asked if they know of other persons with similar symptoms.

Arnon SS et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 2001; 285:1059-1070.



Public Health Response

- True public health emergency
- Support Clinical Management
 - Testing
 - Antitoxin or IG procurement
- Investigate to ascertain public health impact
 - Foodborne, post-therapeutic/cosmetic, or intentional:
 - Single or multiple cases?
 - Common exposure?
 - Implicated food?
 - Mitigate public health impact



Treatment

- Call your local public health department
- Local health department contacts state health department
- State health department consults CDC as indicated
- CDC will work with state health initially
- CDC: 800-CDC-INFO
- Supportive
- Antitoxin
 - Heptavalent now available (A-G)
 - DOD-developed
- Botulism Immune Globulin Intravenous (Human)
 - Infant botulism only
 - California Department of Public Health's Infant Botulism Treatment and Prevention Program Berkeley, CA



Botulism-Prognosis

- The prognosis for case-patients who develop botulinic paralysis is good
 - if secondary complications are prevented
- The greatest improvement is in the first 3 months
- Patients can continue to improve for a year after exposure
- Most require rehabilitative therapy

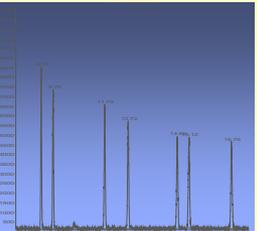
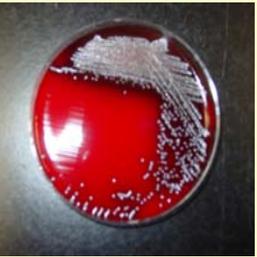


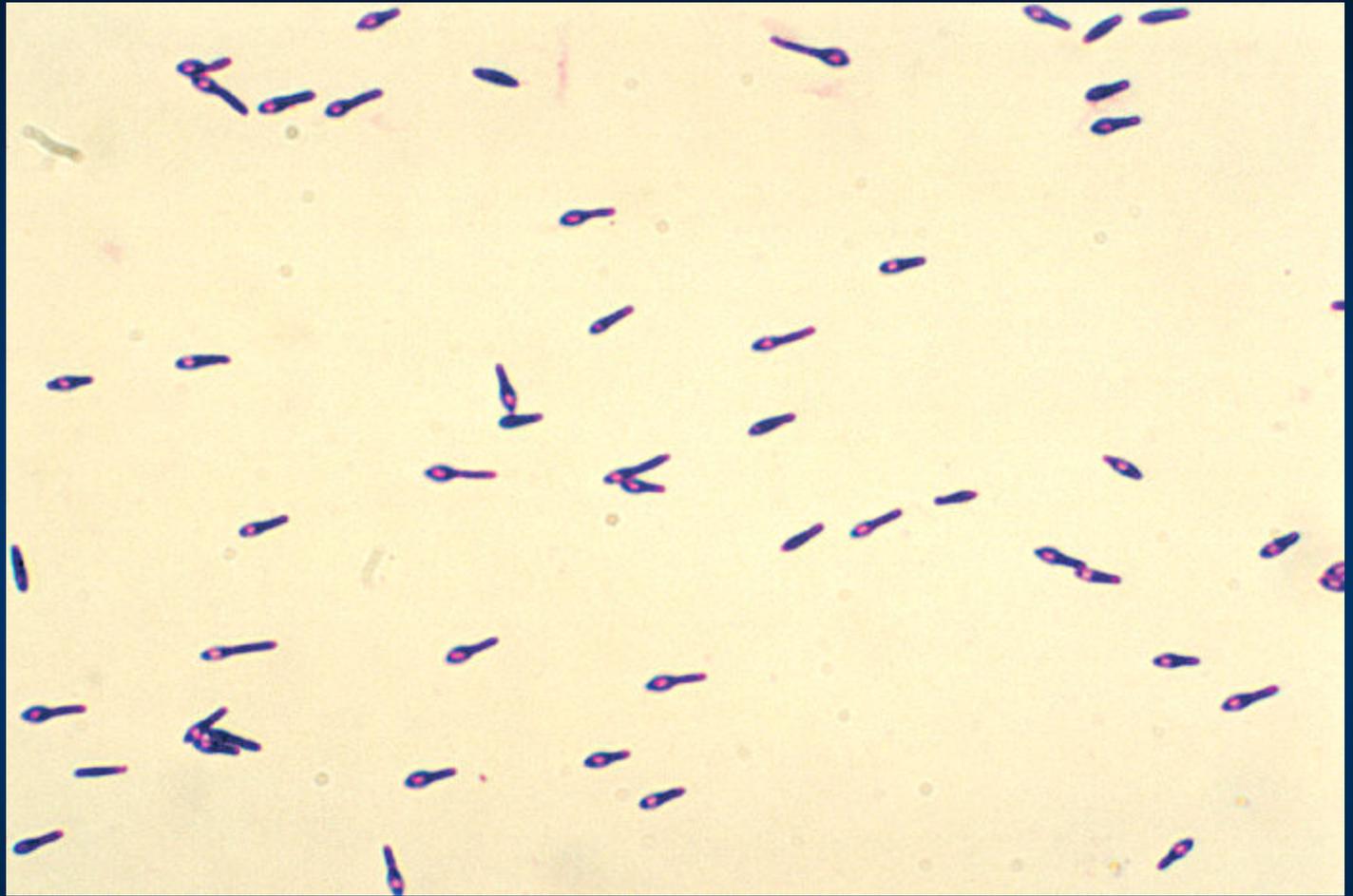
Botulism: Laboratory Aspects

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CDC Public Health Information Library

Botulism toxins

- Seven antigenic types: A, B, C, D, E, F, G
 - Toxin types A, B, and E most commonly associated with human disease
- Toxin produced by *C. botulinum*
 - May be produced by *C. butyricum*, *C. argentinense*, *C. baratii*
- Strains generally only make one toxin
 - Strains may have genes to make more than one type



Botulism toxin

- Most toxic substance known
 - Estimated oral lethal dose: 0.2 – 1 $\mu\text{g}/\text{kg}$
 - Toxin is odorless, colorless, and tasteless
- Toxin secreted as a progenitor toxin
 - 150 kDa protein that must be exposed to protease to cleave to active toxin. 100 kDa and 50 kDa proteins
- Type A most potent. Types B & E cause longest lasting disease



Specimen collection

- Serum
 - 10 - 15 ml. Store at 4-8° C.
- Stool
 - 15 – 25 g. No preservative. Store at 4-8° C.
- Food
 - 100 – 150 g. In original container.
 - Store under original conditions.
- Wounds
 - Anaerobic transport. Room temperature.



Testing methods

- Mouse bioassay
 - Gold standard
 - Limit of detection
- Dig-ELISA
 - Limit of detection
- PCR



Mouse Bioassay

- Serum tested without further processing
- Stool
 - Extract prepared for direct testing
 - Culture enrichment
- Food
 - Extract prepared for direct testing
 - Culture enrichment



Mouse bioassay: serum

Mouse pair	Volume serum	Volume antitoxin	Antitoxin type	Volume injected/ mouse
1	1.0 ml	0 ml	-	0.4 ml
2	1.0 ml	0.25 ml	A	0.5 ml
3	1.0 ml	0.25 ml	B	0.5 ml
4	1.0 ml	0.25 ml	E	0.5 ml
5	1.0 ml	0.25 ml	F	0.5 ml
6	1.0 ml	0.25 ml	ABE	0.5 ml

Mouse bioassay: stool, food, enrichment cultures

Mouse pair	Specimen Volume	Treatment	Antitoxin Type	Volume injected/ mouse
1	1.0 ml	None	None	0.4 ml
2	1.0 ml	Heat	None	0.5 ml
3	1.0 ml	Trypsin	None	0.5 ml
4	1.0 ml	0.25 ml antitoxin	A	0.5 ml
5	1.0 ml	0.25 ml antitoxin	B	0.5 ml
6	1.0 ml	0.25 ml antitoxin	E	0.5 ml
7	1.0 ml	0.25 ml antitoxin	F	0.5 ml
8	1.0 ml	0.25 ml antitoxin	ABE	0.5 ml



Dig-ELISA

- Detects specific toxin
 - Cannot differentiate biologically active from inactivated toxin
 - May exhibit cross-reactivity between toxin types
- Application
 - Food (interference from some matrices)
 - Enrichment cultures
 - Limited information on serum and feces



PCR

- Detects *bot* gene
 - Testing complete in about 4 hours
 - Does not confirm gene expression
 - Does not differentiate living vs. dead organisms
 - Does not detect biologically active toxin
- Direct specimen testing
 - Potential inhibition
- Enrichment cultures
 - Food and environmental sources



Questions

