International Outbreak of Severe Botulism with Prolonged Toxemia Caused by Commercial Carrot Juice

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Background. On 8 September 2006, 3 Georgia residents presented with symptoms of food-borne botulism, a potentially fatal illness caused by Clostridium botulinum neurotoxins.

Methods. Investigators reviewed medical records and interviewed patients and family members. Foods from patients’ homes and samples of the implicated commercial beverage were tested for botulinum toxin and C. botulinum by standard methods.

Results. The patients presented with cranial neuropathies and flaccid paralysis; all patients required mechanical ventilation. The 3 Georgia patients had consumed carrot juice from the same bottle before illness onset. An additional case in Florida and 2 in Ontario, Canada, were subsequently identified in patients who had consumed carrot juice. Serum samples obtained from 5 patients tested positive for botulinum toxin type A—in one patient, 12 days after illness onset, and in another patient, 25 days after illness onset. Carrot juice produced by 1 manufacturer, recovered from patients’ homes in Georgia, Florida, and Ontario, yielded type A toxin. The juice contained no added sugar, salt, or preservative; inappropriate refrigeration likely resulted in botulinum toxin production.

Conclusion. This outbreak was caused by commercially produced, internationally distributed carrot juice that was contaminated with botulinum toxin. When toxemia persists, treatment for botulism should be considered even if diagnosed weeks after illness onset. The implicated pasteurized carrot juice had no barriers to growth of C. botulinum other than refrigeration; additional protective measures for carrot juice are needed to prevent future outbreaks. The US Food and Drug Administration has since issued industry guidance to reduce the risk of C. botulinum intoxication from low-acid refrigerated juices.

Botulism is a neuroparalytic illness caused by neurotoxins of Clostridium botulinum and rare strains of Clostridium butyricum and Clostridium baratii. Dormant C. botulinum spores germinate and produce toxin (types A–G) under the rare confluence of anaerobic conditions; low acid (pH, >4.5), salt, and sugar concentrations; and temperatures >10°C (for most strains). These toxins bind irreversibly to presynaptic nerve endings and inhibit acetylcholine release, resulting in cranial neuropathy and symmetric descending flaccid paralysis, which may progress to respiratory failure [1].

Food-borne botulism is caused by consumption of food that contains botulinum toxin. Most food-borne botulism outbreaks in the United States are attributable to improperly home-canned foods [2]. Commercial retort canning processes, which involve high temperatures and pressures, can eliminate C. botulinum spores [3]. Foods not subject to the retort process rely on combinations of acidity, salt and sugar content, and refrigeration to prevent germination of C. botulinum spores.
Botulism has been caused by nonretorted processed foods that lack such barriers [2, 4, 5].

On 8 September 2006, 3 patients presented to a Georgia hospital with cranial neuropathies, progressive descending flaccid paralysis, and respiratory failure requiring mechanical ventilation. Clinicians immediately notified public health officials, who provided botulinum antitoxin from federal repositories, initiated an epidemiologic investigation, and issued public health alerts. On 25 September, a woman hospitalized since 16 September in Florida was reported as possibly having botulism. On 2 October, 2 Ontario residents, who had been hospitalized in separate hospitals on 25 August and 14 September, were reported to Canadian health authorities as possibly having botulism. We describe this international outbreak of food-borne botulism caused by commercially produced, internationally distributed carrot juice that contained no chemical barriers to C. botulinum germination.

PATIENTS AND METHODS

We interviewed the patients and their contacts about food exposures and collected remnant foods from patients’ homes. We defined a case as illness in a patient with signs and symptoms of botulism, with onset between 1 August 2006 and 1 November 2006, who had consumed carrot juice during the 10 days before illness onset. Cases also had to meet 1 of 3 criteria for laboratory confirmation of botulism, as follows: (1) botulinum toxin identified in a clinical specimen obtained from the patient, (2) C. botulinum identified in a clinical specimen obtained from the patient, or (3) botulinum toxin identified in the same container of carrot juice that the patient had consumed during the 10 days before illness onset. Press releases identifying the implicated beverage were issued by the Georgia Division of Public Health, the Georgia Department of Agriculture, and the US Food and Drug Administration (FDA) on 29 September, and by the Canadian Food Inspection Agency on 30 September. All US state health departments were notified on 15 September and 29 September. Canadian provincial health departments were notified on 30 September and 3 October. State and provincial health departments were requested to report suspected cases to the Centers for Disease Control and Prevention (CDC).

Laboratory tests of clinical specimens and food samples collected from patients’ homes were conducted at the CDC (for US patients) and Health Canada (for Canadian patients). Patient serum specimens, stool specimens, and food samples were tested for botulinum toxin with use of the mouse bioassay [6]. Stool specimens and food samples were also cultured for C. botulinum [6].

Bottles of the implicated beverage collected at the manufacturing plant and from retail stores were tested for botulinum toxin by an in vitro botulinum toxin ELISA at the FDA Southwest Regional Laboratory (Atlanta, GA), by ELISA and mouse bioassay at the National Center for Food Safety and Technology Laboratory (Summit Argo, IL), and by mouse bioassay at the CDC (Atlanta, GA) and the University of Wisconsin (Madison) [6]. The FDA inspected the beverage manufacturing plant. The FDA received from the manufacturer ten 1-L bottles from the implicated lots that were beyond shelf life but had been refrigerated during storage. These bottles were tested for botulinum toxin after incubation at 35°C for 6 days, to simulate lapses in refrigeration. Juice from incubated bottles was inoculated into cooked meat medium and was cultured for aerobic and anaerobic bacteria. Juice odor and bottle appearance were recorded.

RESULTS

Descriptive epidemiology and clinical findings. Outbreak-associated cases were identified in Georgia (3 cases), Florida (1), and Ontario (2). Symptom onsets were 24 August (patient 5; Ontario), 8 September (patients 1–3; Georgia), 12 September (patient 6; Ontario), and 15 September (patient 4; Florida) (table 1). Patient ages had a range of 42–77 years (median, 58 years); 4 patients were female. Patients reported the following neurological symptoms: muscle weakness (6 patients [100%]), dysphagia (5 [83%]), blurred vision (4 [67%]), dysphonia (3 [50%]), and diplopia (3 [50%]). All had severe paralysis and required mechanical ventilation. No other suspected cases of botulism associated with carrot juice consumption were reported to the CDC.

Three patients in Georgia consumed 1 meal together on 7 September, which included juice from a 1-L bottle of Brand X carrot juice, and had illness onset on 8 September. The bottle had a “best by” date of 18 September 2006 and was labeled “keep chilled” (in 1/32” font) on the cap and “keep refrigerated” (in 1/8” font) on the side. The carrot juice bottle and all perishable foods were found stored in a refrigerator at the home of 1 of the affected patients. The kitchen showed no evidence of improper upkeep or hygiene; the refrigerator temperature was not recorded.

The Florida patient had illness onset on 15 September. An opened 450-mL bottle of Brand X carrot juice was recovered from the hotel room where the Florida patient had been staying during the month before hospitalization. The bottle had a “best by” date of 19 September 2006 and a lot number different from that on the bottle associated with the Georgia cases. The bottle was labeled “keep chilled” (in 1/32” font) on the cap and “keep refrigerated” (in 1/16” font) on the side. The hotel room had no refrigerator.

The 2 Ontario patients had illness onset on 24 August and 12 September. An opened 1-L bottle of Brand Y carrot juice was recovered from a refrigerator in the home shared by these 2 patients. The bottle had a “best by” date of 6 September 2006 and was labeled “keep refrigerated” (in 1/32” font) on the side.

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Table 1. Demographic characteristics, time intervals between key clinical events, and clinical outcomes in patients who consumed botulinum toxin–containing carrot juice, 2006.

<table>
<thead>
<tr>
<th>Patient</th>
<th>State or province</th>
<th>Date of symptom onset</th>
<th>Public health officials notified</th>
<th>Time interval</th>
<th>Duration of intubation, days</th>
<th>Clinical outcome 1 year after symptom onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Georgia</td>
<td>8 September 2006</td>
<td>8 September 2006</td>
<td>14</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Georgia</td>
<td>8 September 2006</td>
<td>8 September 2006</td>
<td>15</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Georgia</td>
<td>8 September 2006</td>
<td>8 September 2006</td>
<td>25</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Florida</td>
<td>15 September 2006</td>
<td>25 September 2006</td>
<td>Unknown</td>
<td>&lt;24</td>
<td>&lt;24</td>
</tr>
<tr>
<td>5</td>
<td>Ontario</td>
<td>12 September 2006</td>
<td>2 October 2006</td>
<td>Unknown</td>
<td>~96</td>
<td>48–72</td>
</tr>
<tr>
<td>6</td>
<td>Ontario</td>
<td>24 August 2006</td>
<td>2 October 2006</td>
<td>&lt;24</td>
<td>&lt;48</td>
<td>8</td>
</tr>
</tbody>
</table>

* Patients are numbered in the temporal order in which they came to the attention of public health officials.
The patients’ refrigerator had an appropriate internal temperature of <5°C.

For the 3 Georgia patients, whose time of carrot juice consumption was known, the times from consumption to onset of neurological symptoms were 14, 15, and 25 h, and the times from consumption to intubation were 31, 36, and 33 h, respectively; all 3 patients received treatment with antitoxin <24 h after presentation. The Florida patient and 1 Ontario patient were treated with antitoxin 12 and 44 days after symptom onset, respectively, when the diagnosis of botulism was made and serum test results identified persistent toxemia. The second Ontario patient did not receive treatment with antitoxin, because toxemia was not present at the time of diagnosis.

One year after illness onset, 2 patients (33%) had been discharged home, 2 (33%) were in rehabilitation facilities, and 1 (17%) was still hospitalized. One patient died 90 days (12.9 weeks) after illness onset; the patient had been unresponsive since hospital admission, and ventilatory support was withdrawn. Of the 5 surviving patients, 3 were no longer ventilator dependent and had durations of intubation of 54, 90, and 129 days; the other 2 surviving patients remained ventilator dependent (table 1).

**Laboratory investigation.** For the 3 Georgia patients, botulinum toxin type A was identified in serum and stool samples collected the day after illness onset, and *C. botulinum* type A was isolated from their stool samples. For the Florida patient, botulinum toxin type A was identified in serum samples collected 5, 7, 8, and 12 days after illness onset. A stool specimen was not available for testing. For 1 of the 2 Ontario patients, serum and stool samples collected 22 and 42 days after illness onset were negative for botulinum toxin; no neurotoxin-producing *Clostridia* species were isolated from the stool specimens. For the other Ontario patient, botulinum toxin type A was detected in serum samples collected 25 days after illness onset. Stool specimens collected 41 and 67 days after illness onset were negative for botulinum toxin, and no neurotoxin-producing *Clostridia* species were isolated (table 2).

On 15 September, refrigerated remnant carrot juice recovered from 1 Georgia patient’s home tested positive for botulinum toxin type A. Subsequently, botulinum toxin type A was identified in remnant carrot juice from the bottle that was found unrefrigerated in the Florida patient’s hotel room. The pH of both of these bottles was between 6 and 7. Botulinum toxin type A was also identified in remnant carrot juice from the refrigerated bottle that was found in the home of the Ontario patients. Bottles of the implicated juice from retail stores, which had a mean pH of 6.8, tested negative for botulinum toxin.

**Trace back and production plant investigation.** Brand X carrot juice (consumed by the Georgia and Florida patients) and Brand Y carrot juice (consumed by the Ontario patients) were produced by the same manufacturer in the same plant. This plant produced >1000 gallons of carrot juice per day and distributed carrot juice under 3 different brand labels. Three bottles from 3 carrot juice lots were implicated in this outbreak (2 Brand X lots and 1 Brand Y lot); these lots were distributed to the United States, Canada, and Hong Kong.

Manufacturer’s records revealed that the 2 implicated Brand X lots were processed on the same filling equipment on 2 consecutive days. The implicated Brand Y lot was produced on the same day as the first Brand X lot. Because carrot juice lots from consecutive days may be filled with product originating from the same batch of blended carrots, all 3 toxin-containing bottles could have contained blended carrots from the same batch.

The carrot juice bottles were distributed in cases that were labeled “keep refrigerated.” Manufacturer and distribution records revealed that the toxin-containing bottles did not share the same location during distribution or sale. FDA inspection of the manufacturing plant and production records showed no violations that could explain *C. botulinum* contamination.

After ten 1-L bottles from the implicated carrot juice lots provided by the manufacturer were incubated at 35°C for 6 days, botulinum toxin type A was identified in 5 of the 10 bottles (table 3). The concentration of botulinum toxin in the positive bottles ranged from >10 but <20 to >2000 mouse intraperitoneal lethal dose (MIPLD)~50~/mL.

**Table 2. Time from symptom onset to serum collection and toxin testing results for patients who consumed botulinum toxin–containing carrot juice, 2006.**

<table>
<thead>
<tr>
<th>Patient and time from symptom onset to serum collection</th>
<th>Toxin detected</th>
<th>Serum toxin concentration, MIPLD<del>50</del>/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Not determined</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Not determined</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>&gt;20</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 days</td>
<td>Yes</td>
<td>&gt;200</td>
</tr>
<tr>
<td>7 days</td>
<td>Yes</td>
<td>1800</td>
</tr>
<tr>
<td>8 days</td>
<td>Yes</td>
<td>&gt;200</td>
</tr>
<tr>
<td>12 days</td>
<td>Yes</td>
<td>&gt;200</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>22 days</td>
<td>No</td>
<td>...</td>
</tr>
<tr>
<td>42 days</td>
<td>No</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 days</td>
<td>Yes</td>
<td>Not determined</td>
</tr>
<tr>
<td>41 days</td>
<td>No</td>
<td>...</td>
</tr>
<tr>
<td>60 days</td>
<td>No</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** MIPLD~50~, mouse intraperitoneal lethal dose~50~.

*a* Serum samples obtained on days 5, 7, 8, and 12 were sent for laboratory testing simultaneously.

Manufacturer’s records revealed that the 2 implicated Brand X lots were processed on the same filling equipment on 2 consecutive days. The implicated Brand Y lot was produced on the same day as the first Brand X lot. Because carrot juice lots from consecutive days may be filled with product originating from the same batch of blended carrots, all 3 toxin-containing bottles could have contained blended carrots from the same batch.
intraperitoneal lethal dose 50 (MIPLD50) per mL. Bottles containing botulinum toxin did not have an unpleasant odor or unusual appearance indicative of gas production by bacterial organisms. Four of the 5 bottles that did not contain botulinum toxin after incubation had sour odors, and 3 of these 5 bottles had gas production.

**DISCUSSION**

We report an outbreak of food-borne botulism from commercially produced, internationally distributed carrot juice that affected 6 patients in 2 US states and 1 Canadian province. In previously reported food-borne botulism case descriptions, patients with type A botulism had a median incubation period of 1 day and a mean duration of intubation of 58 days [7, 8]. In this outbreak, clinical illness was marked by rapid onset and protracted paralysis that required mechanical ventilation (for >1 year in 2 of 6 patients); in 3 patients, this occurred despite prompt antitoxin therapy, which indicates extremely high levels and persistence of toxin in the patients’ bloodstream.

The concentrations of botulinum toxin in 2 of the carrot juice bottles that were consumed by patients were 100 MIPLD per mL (J.A., unpublished data) and 100,000 MIPLD per mL (6.6 × 10^2 MIPLD 50 per mL [S.M., unpublished data]). Before this outbreak, the highest concentration of toxin reported in food was 3.2 × 10^3 MIPLD 50 per g of a potato dip [9]. The high concentration of botulinum toxin in 1 of the carrot juice bottles involved in the current study and the feasibility of consuming large volumes of juice, compared with other foods, could explain the rapid progression and long duration of paralysis in 3 patients who received prompt antitoxin therapy and the persistent toxemia in 2 other patients.

Botulinum toxin concentration in serum samples collected <18 h after exposure has been reported to be as high as 160 MIPLD 50 per mL [10]. One patient in the current outbreak had a toxin level in serum samples obtained 8 days after symptom onset of 1800 MIPLD 50 per mL, >10 times higher than the previous highest reported level, despite being collected days after exposure. An estimation of 3000-mL total plasma volume would yield a total circulating toxin load of 5.4 × 10^9 MIPLD 50 on day 8 after symptom onset in this patient, indicating that this patient likely had an extremely high serum toxin level at the time of symptom onset. The standard recommended dose of botulinum antitoxin containing 7500 IU of anti-A antitoxin can neutralize 7.5 × 10^2 MIPLD 50 of botulinum toxin. For this patient, the standard recommended dose of antitoxin may not have been sufficient if this patient had received a diagnosis of botulism sooner after illness onset. This case suggests that the standard antitoxin dose, although appropriate for this patient at the time of treatment and for most patients exposed to highly toxic foods, may not be adequate for patients who ingest very large amounts of botulinum toxin. In such circumstances, serum samples collected 24 h after antitoxin treatment can be tested to determine whether toxin is still present.

Botulinum toxin is most commonly detected in serum specimens obtained shortly after toxin ingestion; it is detected in <20% of serum specimens obtained 6 days after toxin ingestion [7]. Persistence of botulinum toxin in patient bloodstream has been reported 25 days after toxin ingestion in a patient with food-borne botulism [11]. Two patients in the current outbreak had toxin in bloodstream 12 and 25 days after symptom onset. These findings could be attributable either to ingestion of high doses of toxin or to in vivo toxin production after intestinal colonization with *C. botulinum*, a rare cause of botulism in adults. Sustained shedding of *C. botulinum* in the stool is considered to be an indication of colonization [12]. Stool samples collected from the patient with toxin in bloodstream 25 days after symptom onset were negative for botulinum toxin and did not contain *C. botulinum*, suggesting that sustained toxemia more likely resulted from ingestion of high doses of toxin than from in vivo toxin production.

Both patients with prolonged toxemia were severely paralyzed and dependent on mechanical ventilation at the time that they were found to be toxemic. The 2 patients were treated with antitoxin, one at 13 days and the other at 46 days after onset of neurological symptoms, once they were identified as having clinical symptoms consistent with botulism and were found to be toxemic. Serum from 1 patient was tested after antitoxin treatment and was found to be negative for botulinum toxin. Before this outbreak, antitoxin treatment was generally not administered if a patient was identified with symptoms consistent with botulism >7 days after onset of neurological symptoms and if symptoms were not progressing. The finding in this outbreak that toxemia may be present for >7 days after symptom onset suggests that antitoxin treatment should be considered in patients with suspected botulism and stable neu-
rological function weeks into the course of illness when ingestion of a high dose of toxin is suspected. Although antitoxin treatment in the setting of prolonged toxemia may prevent further binding of circulating toxin, clinical responses in severely paralyzed patients need to be further investigated.

No laboratory-confirmed cases of botulism with unknown source were reported to the CDC in 2006 [13]. Carrot juice produced by the same manufacturer of the juice that caused this outbreak was consumed by 2 California patients with laboratory-confirmed botulism in August 2004 and May 2006 (C. Wheeler, California Department of Public Health, personal communication). Before illness onset, those patients consumed two different brands of carrot juice produced by the manufacturer of the juice that caused this outbreak, but the juice was not available for testing, and the association was not confirmed. These cases suggest rare but recurring botulinum toxin contamination of carrot juice produced by this manufacturer.

The contaminated carrot juice contained no barrier other than refrigeration to prevent the growth of <i>C. botulinum</i>. Carrot juice is naturally a low-acid (pH, 6.8), low-salt, and low-sugar liquid. Once placed in the anaerobic environment of a sealed plastic bottle, it presents no intrinsic barrier to the germination of naturally present <i>C. botulinum</i> spores. No acidifying preservative, salt, or sugars were added to the product that caused this outbreak. Because this outbreak occurred as a result of contamination with <i>C. botulinum</i> type A (minimum temperature for growth, 10°C) with subsequent growth and toxin production, it is very likely that there was failure to maintain a temperature <10°C along the chain of production, distribution, retail, purchase, and consumption for the juice bottles associated with this outbreak. The 3 implicated juice bottles were kept at appropriate temperatures before distribution, and they did not share the same location during distribution or retail. This suggests that refrigeration failures must have occurred separately for each bottle between production and consumption.

In the 1980s, commercially produced jars of garlic packed in oil, lacking barriers of acidity, salt, or sugar, caused a series of botulism outbreaks [4, 5, 14]. After an FDA requirement for the addition of an acidifying preserving agent, no further outbreaks occurred from this product. In response to the carrot juice outbreak, in June 2007, the FDA modified its guidance for refrigerated low-acid juices to recommend adding a validated juice-treatment method, such as acidification or appropriate thermal treatment, to decrease the risk of <i>C. botulinum</i> contamination, should any breaches in refrigeration occur [15]. Given the difficulty of maintaining refrigeration for vast volumes of internationally distributed juice, adoption of these additional controls will help prevent similar outbreaks. After this outbreak, the manufacturer of the implicated carrot juice, the largest carrot juice distributor in the United States, revised its manufacturing processes to destroy spores of the most heat-resistant forms of <i>C. botulinum</i> in its low-acid juice products.

This investigation demonstrates that carrot juice and other processed foods with no natural barriers to <i>C. botulinum</i> germination require additional chemical or thermal barriers. Extremely high serum toxin levels involving profound, protracted paralysis despite timely antitoxin treatment may result from consumption of high levels of toxin. The standard dose of licensed antitoxin may not adequately neutralize toxin in patients who consume extremely large amounts of botulinum toxin; toxemia may persist for weeks in such patients if diagnosis and antitoxin treatment are delayed. This outbreak highlights the importance for clinicians of considering the diagnosis of botulism, particularly during outbreaks. Clinicians who suspect botulism should immediately call the state or provincial health department’s 24-h emergency telephone number to arrange for clinical consultation and antitoxin release.

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