

Wound botulism caused by *Clostridium subterminale* after a heroin injection

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Abstract

Botulism is caused by toxin production from many species of *Clostridium*, most commonly *Clostridium botulinum* as well as *C. baratii* and *C. butyricum*. Development of wound botulism is associated with injection drug users but has also been described in traumatic injuries with exposure to soil. A patient presented to the emergency department with a complaint of descending, progressive weakness. He recently reported skin popping with heroin injections. Heptavalent botulinum antitoxin was obtained from the [Center for Disease Control and Prevention (CDC)]. On hospital day seven, the anaerobic wound cultures resulted with growth of *Clostridium subterminale*.

Introduction

Botulism is an illness caused by toxin production from many species of the *Clostridium* genus of bacteria, most commonly *Clostridium botulinum*, *C. baratii*, and *C. butyricum*. These bacteria are anaerobic, spore-forming, Gram-positive organisms found naturally in the soil. The different types of botulism include foodborne botulism from improperly canned or stored foods, infant botulism and adult intestinal toxemia from ingestion of botulinum neurotoxin-producing species of *Clostridium* in infants and adults, respectively, wound botulism, and iatrogenic botulism as a result of cosmetic or therapeutic botulinum toxin overdoses. Wound botulism can occur when botulinum neurotoxin-producing species of *Clostridium* infect and germinate in wounds and begin producing toxins. Wound botulism presents most similarly to foodborne botulism with descending flaccid paralysis of facial, swallowing, and respiratory muscles, with the exception that it does not typically have accompanying gastrointestinal symptoms.¹⁻³ Development

of wound botulism is commonly associated with injection drug users but has also been described in traumatic injuries with exposure to soil.

Case Report

A 33-year-old male had recently presented to another hospital in the area just prior to admission at our hospital for weakness, fatigue and bilateral hip and leg abscesses. At that time he elected to be treated for cellulitis as an outpatient and was prescribed cephalexin 250 mg by mouth four times daily and sulfamethoxazole-trimethoprim 400-80 mg by mouth twice daily for ten days. He then presented to our hospital two days later with a chief complaint of difficulty swallowing and progressive weakness which he states he had for one week. His past medical history included daily heroin use, administered by *skin popping* or injecting the drug under the skin either intradermally or subcutaneously, and untreated hepatitis C. On presentation to our hospital, the patient was only able to open his eyelids 2-3 mm wide and had difficulty keeping them open, diplopia, difficulty swallowing and pooling of secretions after 1-2 words, voice changes, difficulty holding his head up and proximal upper extremity weakness. Strength in his upper extremities were 4/5. Initial vital signs included: blood pressure 136/80 mmHg; pulse rate 106 beats/min; respiratory rate 19 breaths/min; oral temperature 36.5°C (97.7°F); and room air pulse oximetry 98%. Five deep cavity abscesses were incised and drained from the patient's hips and thighs, and standard and anaerobic wound cultures were collected. After a few hours, the weakness became more pronounced in the patient's neck and extremities and breathing became very shallow. The decision was made to intubate the patient in the emergency department for airway protection and impending respiratory failure before transferring him to the [medical intensive care unit (ICU)]. A urine drug screen was positive for amphetamines, opiates, and acetone.

The constellation of symptoms seen in the emergency department was suggestive of botulism, with other differential diagnoses including Guillain-Barré Syndrome and myasthenia gravis. He reported not having eaten canned food that had been bulging and had not traveled outside of the country recently. Therefore, the suspicion was for possible wound botulism. The Maricopa County Department of Public Health was contacted, and receipt of heptavalent botulinum

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antitoxin (A, B, C, D, E, F, G) –BAT® Equine was coordinated directly with the [Centers for Disease Control and Prevention (CDC)]. The antitoxin arrived by freight air transport the next morning on hospital day two and was administered via infusion approximately nineteen hours after presentation to the emergency department. Serum, stool and wound cultures were sent to the CDC for analysis. Wound cultures were also sent to the hospital's lab for analysis. In addition, vancomycin and piperacillin-tazobactam, were started for broad antibiotic coverage including possible [methicillin-resistant *Staphylococcus aureus* (MRSA)].

In the medical ICU, the patient's weakness plateaued and antibiotics were deescalated to vancomycin and ampicillin-sulbactam for continued coverage of his complicated skin-soft tissue infection. After three days in the ICU (hospital day four), a tracheostomy was performed for the expected long recovery time and a PEG

tube was inserted. The patient was then transitioned to oral antibiotics, amoxicillin-clavulanate 875 mg by mouth twice daily and sulfamethoxazole-trimethoprim 800-160 mg, two tablets by mouth twice daily for two weeks. On hospital day seven, the anaerobic wound cultures analyzed by the hospital's lab resulted with growth of *Clostridium subterminale*. On hospital day ten, results from the CDC serum analysis reported toxin A which was identified using MALDI-TOF mass spectrometry, the wound culture analyzed by the CDC did not report botulinum toxin, and the stool was not analyzed.

After a twelve-day hospital stay, the patient was discharged to a skilled nursing facility. He continued to have bilateral ptosis, difficulty swallowing and generalized weakness. He continued to have 4/5 bilateral deltoid muscle strength but 5/5 strength in all other major muscle groups. He had a tracheostomy placed on hospital day 5 and was being weaned off the ventilator at time of discharge.

Discussion and Conclusions

Wound botulism is caused by the growth of *Clostridium* bacteria, most commonly *Clostridium botulinum*, and subsequent toxin production in a wound. Many *Clostridia* species including: *C. botulinum*, *C. butyricum*, *C. argentiense*, *C. baratii*, *C. subterminale*, *C. hastiforme*, *C. sporogenes*, and *C. perfringes*, have been shown to produce eight different toxins, A, B, C-a, C-b, D, E, F, and G. However, only certain toxin types have been associated with human botulism which include type A, B, E and F toxins with type A, B and E accounting for the majority of cases. *C. botulinum* has been shown to produce all four toxin types. *C. baratii* has been shown to produce type E toxin and *C. butyricum* has been shown to produce type F toxin. Type A toxin is most prevalent in the western United States and type B in the eastern United States and Europe. Type E is associated with the consumption of raw marine animals around the world.² These toxins are taken in by presynaptic nerve endings where they irreversibly cleave to soluble N-ethylmaleimide sensitive fusion protein attachment receptor which prevents acetylcholine-containing vesicles from fusing to the cell membrane and releasing the neurotransmitter into the synapse. This results in a classic flaccid paralysis in patients with botulism.²

In our particular case, the organism isolated was of unique interest as it is not commonly described as pathogenic nor

isolated from wounds. To our knowledge, this is the first case reporting a *Clostridium subterminale* positive wound culture with type A toxin identified in the serum sample. *C. subterminale* is a species that is similar to Group IV *Clostridia* and has been shown to be able to produce typeG toxin, which is not responsible for human illness and to express the gene capable of producing type B toxin, however, has not been shown to actually produce this toxin.⁴⁻⁶ One study which focused on *Clostridia* infections in post-traumatic wounds identified five cases where the growth of *C. subterminale* was found associated with soil contamination.⁷ *C. subterminale* has been previously reported in immunocompromised patients undergoing chemotherapy, with three bacteremia cases reported.⁸⁻¹⁰ A separate case of bacteremia in an immunocompetent patient was found after an esophageal rupture.¹¹ Additionally, there were two cases reported *C. subterminale* in pleuropulmonary infections, two cases of soft tissue infection, and one case in an open fracture.¹²⁻¹⁵ None of the studies mentioned above provide information regarding neurologic exam findings or toxin identification. Based on these case reports and available literature examining the ability of *C. subterminale* to produce botulinum toxin it is possible that our patient had a co-infection with another *Clostridia* species that was not identified in the sole wound culture that was obtained.

The CDC has compiled an annual surveillance study since 2001 of all reported cases of botulism and provide data on the number of botulism cases by type, toxins found, and states where the cases occurred. The most recent CDC Botulism Annual Survey in 2016 reported twenty-four cases of confirmed wound botulism (12% of all botulism cases that year) and an additional two cases of probable wound botulism. Twenty-three (95.8%) of the patients with confirmed wound botulism were injection drug users (22 injected black tar heroin and 1 injected methamphetamine).¹⁶ There has been a steady number of wound botulism cases reported since 2001 with an average of 23 cases per year. The majority of wound botulism cases in 2016 (15 cases) occurred in California, with the next highest amount in New Mexico (3 cases). Other states where cases were reported include Arizona, Colorado, Utah, Texas, New Jersey, and Hawaii with one case each.

A 1998 study published in JAMA looked at twenty-six cases of wound botulism occurring in California from 1994 to 1996 with the intent of finding common risk factors among these cases. They compared these cases with 110 control

patients who were enrolled in methadone programs in California and had never had wound botulism. Both groups reported similar rates, 96% and 97% respectively, of [black tar heroin (BTH)] use. Their results showed that a significantly higher percentage of patients with wound botulism were injecting BTH by skin popping either subcutaneously or intramuscularly than their control counterparts (92% vs 44%, $P < 0.001$).¹⁷ Other studies have continued to look at wound botulism in injection drugs users, especially those using BTH, and have found similar results.¹⁸

Early recognition of the signs and symptoms of botulism is important. Due to neuroparalytic effects of the toxin produced by *Clostridium* bacteria, there is a cluster of symptoms typical of patients presenting with botulism. The most classic signs are cranial nerve palsies and descending flaccid paralysis. The eyes are often reported as being affected first with signs of diplopia and ptosis. This is frequently followed by facial paralysis and paralysis of the muscles associated with chewing and swallowing resulting in difficulty swallowing and forming words. Sometimes, after that, a proximal to distal progression of paralysis occurs in the arms and legs. If paralysis continues, the toxin may eventually affect the diaphragm and accessory breathing muscle resulting in respiratory distress or failure. Respiratory failure may occur earlier in the illness due to upper airway collapse or aspiration.^{1,2} Often, this results in patients being intubated and a subsequent stay in the ICU. Wound botulism does not frequently involve the gastrointestinal symptoms that would be seen in foodborne botulism.³

Due to the type of symptoms present in botulism infections, there are a number of differential diagnoses that need to be considered. Guillain-Barré syndrome is an autoimmune disease that demyelinates neurons and causes an ascending paralysis. However, the Miller Fischer variant of Guillain-Barré syndrome presents with a descending paralysis, closer mimicking that of botulism. Myasthenia gravis is an autoimmune neuromuscular disease that results in weakness of certain muscle groups, sometimes including facial and respiratory muscles. Bilateral or brainstem strokes can also cause similar symptoms such as facial drooping, limb weakness, and breathing difficulties.^{1,19} Ruling out other differential diagnoses is important, however, until botulism can be definitively ruled out, treatment should be considered.

The treatment of botulism includes the administration of botulinum antitoxin. For wound and foodborne botulism, this refers

specifically to the equine-derived, heptavalent antitoxin that covers types A, B, C, D, E, F, and G toxins. This antitoxin is supplied by the CDC. Local or state health departments and the CDC are available 24 hours per day 7 days per week for urgent clinical consultations to discuss whether botulism is likely and whether treatment with botulinum antitoxin is warranted. The antitoxin works by binding to and neutralizing any free botulinum toxin and preventing them from binding to nerve endings blocking the development of paralysis.²⁰ Administration of the antitoxin does not affect the toxin that is already bound, therefore, it does not reverse any paralysis that is already developed but will prevent further paralysis from forming. There have been no randomized control trials examining equine botulinum antitoxin as a treatment in humans

Early recognition and treatment is very important as benefits of early antitoxin treatment have been shown. One review published in 2003 looked at seven published, confirmed cases of wound botulism in order to identify the timing of antitoxin administration and subsequent outcomes. Two patients received the antitoxin therapy in four days of symptom onset, four patients within eight to fourteen days, and one patient never received antitoxin. The group of four patients who had treatment initiation after four days of symptom onset had longer lengths of hospital stay, were less likely to be ambulatory on discharge, and went to either a nursing home or rehabilitation facility.²¹ A second study from 2009 reviewed twenty-nine cases of wound botulism. The primary objective of this study was to identify factors associated with mechanical ventilation needs, length of ICU stay, length of hospital stay, complications and death. All of the patients were injection drug users who admitted to using heroin via skin popping. The results of this study showed that increasing the time from presentation to antitoxin administration was associated with an increased length of stay in the ICU.²² A third study reviewed 249 patients with confirmed botulism who received the equine-derived heptavalent botulinum antitoxin. This study showed a significantly shorter length of hospital stay (15 vs 25 days) and ICU length of stay (10 vs 17 days)

for those patients who were treated early (≤ 2 days) verses those who were treated later.²³

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