



TECHNICAL REPORT

Scientific advice on type F botulism

ECDC TECHNICAL REPORT

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Lara Tavoschi.

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Abbreviations

BoNT	Botulinum neurotoxin
BAT-AB	Botulinum antitoxin AB
BAT-E	Botulinum antitoxin E
CDC	US Centers for Disease Control and Prevention
EMA	European Medicines Agency
EPIS	The Epidemic Intelligence Information System
EWRS	Early Warning and Response System
EU/EEA	European Union/European Economic Area
HBAT	Heptavalent botulinum antitoxin, produced by Cangene Corporation
TESSy	The European Surveillance System

Executive summary

In 2011, a familiar cluster of type F botulism caused by *Clostridium baratii* was identified in Spain. The currently available treatment, trivalent antitoxin ABE, has no proven effectiveness on this rare form of botulism. In 2010, a new heptavalent antitoxin (HBAT) became the only available treatment for non-infant botulism in the United States. In consideration of the above, Spain submitted an official request for scientific advice to ECDC on the availability and effectiveness of different types of antitoxins to neutralise type F toxin. ECDC performed a literature review and consulted with the European Medicines Agency (EMA) to produce this document.

In brief, the quality of the evidence available regarding effectiveness of ABE antitoxin against botulism F is limited to experimental studies in animals, human case-reports and observational descriptive studies. Evidence based on studies of effectiveness that included a comparison group (neither observational, nor randomised control studies) is missing. The available evidence points towards the lack of effectiveness of bivalent AB antitoxin or trivalent ABE antitoxins for the treatment of type F botulism. In addition, there is very limited clinical evidence of cross-neutralisation between anti-toxin E and neurotoxin F. According to the information available at the time of this report there is no heptavalent botulinum antitoxin currently approved as a medicinal product in the EU. However it cannot be excluded that Member States may have a heptavalent botulism antitoxin available for emergency situations.

The recent cases of botulism type F in the EU, and the most recent discovery of a new toxin type H in the United States, raises some concern on the availability of effective treatment and preparedness at the EU level, which should be addressed by the competent institutions. Further monitoring of the epidemiological relevance of botulism type F in the EU, such as the inclusion of data on neurotoxin type and/or *Clostridium sp.* in the enhanced surveillance for botulism at EU level, should be considered.

Specific question

Request description

- Is the heptavalent botulinum antitoxin available in Europe?
- Which procedures need to be followed in order to obtain it?
- Should the heptavalent botulinum antitoxin replace the ABE antitoxin?
- Should the heptavalent botulinum antitoxin be used for botulism type F?
- Is ABE antitoxin effective against botulism type F?
- Is there any evidence of cross-neutralisation between antitoxin E and toxin F?

Evidence assessment

A scientific literature search was undertaken to identify the best available evidence from Cochrane Library, Medline (Pubmed) and Embase (embase.com) on 11 and 12 July of 2013. A general search on Cochrane Library was submitted to identify systematic reviews on the topic. Different specific search strategies were developed for Embase and Medline. Two searches were submitted to each electronic database, one for the epidemiological aspects related to the Botulinum type F epidemiological aspects, and the other one for Botulinum type F and antitoxins. Strategies combine terms in controlled language in each database (MeSH and Emtree terms) and text words to balance their sensitivity and relevance. No language or date restrictions were applied. Search strategies are available in Annex 1.

In addition, the websites of ECDC, Public Health England and the US Centers for Disease Control and Prevention (CDC), were accessed to retrieve epidemiological data and other grey literature on botulism. The Epidemic Intelligence Information System (EPIS) and the Early Warning and Response System (EWRS), as secure and confidential platforms, maintained by ECDC, were accessed to review notifications from the EU food- and waterborne network and exchange of information on events and control measures respectively.

Surveillance data was reviewed from the mandatory notifiable surveillance systems for botulism from 29 EU/EEA countries, by accessing the European Surveillance System (TESSy)^{i,ii}.

i Decision no 2119/98/EC of 24 September 1998, and; Decision 2012/506/EU of 8 August 2012

ii Regulation (EC) No 851/ 2004 of 21 April 2004

Scientific advice

Background and epidemiology

Botulism is a serious illness caused solely by the action of serologically distinct neurotoxins (BoNTs A-G) produced by the bacteria *Clostridium sp.* Virtually all known human cases have been caused by toxin types A, B, E, and more rarely F. In the vast majority of cases the toxin-producing organism is *Clostridium botulinum*. Rare cases have been caused by *Clostridium baratii*, which produces type F toxin and *Clostridium butyricum*, which produces type E toxin [1-5]. Most recently a new toxin type, namely toxin type H (BoNT H), has been discovered in the United States. The new toxin was produced by *Clostridium botulinum* strain isolated from a case of infant botulism [6,7].

Clostridium species produce spores that are ubiquitous in the environment, surviving for extended periods of time under adverse environmental conditions. Under appropriate anaerobic conditions, spores may germinate, and the resultant vegetative cells may produce neurotoxin. Contamination with neurotoxins has been described in foods and in association with improper canning (particularly home canning); inappropriate fermentation of meat/sausage, bean curd, and fish; and preservation of a variety of products under oil or conditions that promote an anaerobic environment [8,9]. Ingestion of contaminated food, or, more rarely, infection of an exposed wound or growth in an immunologically immature intestinal tract (i.e. infant botulism) or adult intestinal colonisation can produce the clinical syndrome of botulism [1,5,9].

Botulism is characterised by progressive flaccid paralysis of motor and autonomic nerves, and it usually occurs in a proximal to distal pattern. The clinical picture may vary from vomiting and headache to double vision and paralysis of muscles leading to respiratory failure, and finally death. Severe symptoms require intensive-care treatment and administration of anti-toxin. Even when treatment is available, the case fatality ratio averages 30–65%. Once clinical symptoms appear, the neurotoxin is considered to have irreversibly bound to receptors and entered the cell, blocking acetylcholine release. The administration of antitoxin can neutralise unbound neurotoxin, but cannot reverse existing symptoms [10].

Type F botulism was first described in 1960 following an outbreak occurring in Denmark involving liver paste [11]. In the United States type F botulism was first reported in 1966 during a foodborne outbreak [12]; and in 1979 in an infant botulism case [13].

The Centers for Disease Control and Prevention (CDC) maintains active surveillance for botulism cases in the United States. A detailed review of adult type F botulism cases between 1981 and 2002 based on medical charts and laboratory data from CDC and local health departments was performed in the United States [14]. Out of 1 269 cases of botulism reported, 13 (1%) were adult type F and none were part of an outbreak. A toxigenic *Clostridium baratii* was identified in nine (69%) of 13 cases. The eleven cases for which clinical data were available, were characterised by a fulminant course with rapid progression to respiratory failure and paralysis, but short duration. All patients showed spontaneous signs of improvement in neuromuscular function on average on day eight after hospitalisation. The mean duration of ventilatory support and hospitalisation was 24 and 30 days respectively. No deaths were reported. In only one case was a possible foodborne etiology identified in a leftover of spaghetti and tuna, while five cases had a history of gastrointestinal disease or invasive surgery [14].

In more recent years, 1 548 cases of botulism intoxication were reported to CDC in the period 2001–2011. Of these, 19 (1%) were classified as type F botulism cases (one of which was classified as type Bf). The majority were adult cases (12 or 63%). Of these, nine (75%) were exposed to an unknown source, two (17%) were food-borne and one (8%) was a case of adult colonisationⁱ.

ECDC maintains a surveillance system for botulism cases in EU/EEA countries. All Member States (except for Belgium), have a comprehensive and compulsory surveillance system. At present data on BoNT type are not collected. In the period 2006–2012, 777 confirmed cases of botulism were reported to TESSy from 29 Member States. Of the 770 cases for which gender was reported, 60.4% were male, and; of the 742 cases with reported age, the average age was 38 years and 6.9% were infant cases (<1yr). In the same period, 18 clusters/single case reports for a total of 55 cases were reported to ECDC through the EPIS and EWRS platforms to be associated mainly with food consumption but also with possible animal contact. Only for nine (50%) of the episodes was BoNT type reported, and none of them were reported to be associated with type F neurotoxin. Nevertheless in 2011, an outbreak caused by botulinum toxin type F affecting five members of a Chilean family was reported in Barcelona, Spain [15].

ⁱ US Centers for Disease Control and Prevention. Botulism surveillance.
http://www.cdc.gov/national-surveillance/botulism_surveillance.html

Environmental studies report the presence of BoNT F in soil samples in Argentina, although BoNT A is the most common type and the only one detected in infant botulism cases in Argentina between 1982 and 2005 [16]. Studies on 294 honey and honey-comb samples from Denmark, Norway and Sweden using a multiplex-PCR method detected BoNT presence in 83 samples, of which two were positive for type F [17].

Botulinum neurotoxin overview

The seven serologically distinct and fully characterised *Clostridium botulinum* neurotoxins (BoNTs A-G) are zinc metallo-endopeptidases which block the neurotransmitter release by cleaving an essential receptor complex with unique substrate specificity [18]. They share structural similarity, although the amino acid sequence identity of the BoNT serotypes A to G range from approximately 35 to 70% [19,20].

In depth phylogenetic analysis of the BoNT F genes revealed the existence of seven subtypes (F1 to F7) with inter-subtype nucleotide diversity up to 25%. Of these, subtype F7 was composed exclusively of BoNT F genes from *Clostridium baratii* strains [21]. Further studies showed that BoNT F exhibits a strict requirement for residues for substrate recognition that distinguishes BoNT F from other zinc endoproteases, including BoNTs A and B [22,23].

The existence of considerable sequence variability within BoNT serotypes can significantly affect antibody binding and neutralisation [20,24]. There are reports of various levels of cross neutralisations of BoNT F with antitoxin E in animal models [3,4,25,26]. Two of these are case reports of type F botulism associated with *Clostridium baratii* previously mentioned [3,4,14]. In mice bioassay, the lethality of inoculated serum samples was neutralised by type F antitoxin and cross-neutralised with lower efficiency by type E antitoxin [3,4]. In a case report from Sobel et al., also associated with *Clostridium baratii*, no protection was conferred on mice by antitoxins to botulinum toxins A, B, or E [27].

Finally, a recent study explored the potential of human monoclonal antibodies (mAb) for the cross-neutralisation of BoNTs. Two mAbs were identified capable of binding with high affinity different BoNTs in vitro and capable of neutralising BoNT B and E in vivo [24].

Botulinum antitoxin and case reports of botulism type F

In 2010, CDC announced the availability of a new heptavalent botulinum antitoxin (HBAT, Cangene Corporation) through a CDC-sponsored Food and Drug Administration Investigational New Drug protocol. HBAT replaced a licensed bivalent botulinum antitoxin AB and an investigational monovalent botulinum antitoxin E (BAT-AB and BAT-E, Sanofi Pasteur). As of March 13, 2010, HBAT became the only botulinum antitoxin available in the United States for naturally occurring non-infant botulism [28]. Two case-reports were retrieved on the exclusive use of HBAT in type F botulism. One describes an adult case of initial recovery and rebound of intestinal colonisation botulism after administration of the heptavalent botulinum antitoxin [29]. The second one reports a case of difficult diagnosis, such as the HBAT was only administered on day 17 after hospitalisation, once neurologic improvements had been noticed [30].

Globally, few cases of adult type F botulism are reported in literature. In three single cases reported in the USA in the period 2002–2009 the patients were treated with bivalent AB antitoxin or trivalent ABE antitoxins. In all cases the administered antitoxins did not halt the progression of the paralysis. The patients gave gradual signs of spontaneous recovery after an average of eight days after hospitalisation. All three cases were associated with *Clostridium baratii* [3,4,27]. In another case, delayed diagnosis of botulism F was not followed by the administration of antitoxin, and the patient showed neurologic improvements after a week from hospitalisation [2]. A review of 12 cases of type F botulism in the USA reports that administration of AB or ABE antitoxin did not halt the course of the disease, nor did the additional administration of heptavalent antitoxin in two cases. No clear relationship was identified between timing, type of antitoxin administration and appearance of first signs of recovery on average on day eight after hospitalisation [2-4,14]. Conversely a case of intestinal toxic infection by *Clostridium botulinum* type F initially treated with bivalent botulinum antitoxin AB, showed rapid and significant decrease of BoNT serum level after 24 hour from the administration of polyvalent antitoxin ABEF [31].

According to a report of a food-related type F botulism outbreak due to *Clostridium baratii*, involving five adults in Spain, administration of antitoxins to botulism toxin types A, B and E within 24 hours of hospitalisation did not halt the progression of disease [15]. Finally, in an outbreak caused by *Clostridium botulinum* subtype Af (i.e. producing both toxin A and F but in different quantities) in Argentina, the patient died despite the antitoxic and supportive treatment with polyvalent antiserum administered containing A, B and E antitoxins [32].

Conclusion

Is the heptavalent botulinum antitoxin available in Europe?

A heptavalent antitoxin has been available in the United Kingdom through the Scottish National Blood transfusion Service-SNBTS / MoD Botulinum antitoxin. According to the most recent guidelines on botulism management [33], this antitoxin is not sourced anymore, although some repository centres may have SNBTS/MoD antitoxin still in stock.

According to the information available at the time of this report there are no other heptavalent botulinum antitoxins currently approved in the EU/EEA. However it cannot be excluded that Member States may have a heptavalent botulism antitoxin available for emergency situations.

Which procedures need to be followed in order to obtain it?

The procedures to obtain the heptavalent botulinum antitoxin are subject to Member States national laws and might be different from one Member State to another. National medicines agencies should be consulted in the Member State where such need emerges.

Should the heptavalent botulinum antitoxin replace the ABE antitoxin?

This question is related to clinical management. It should be addressed to clinical and risk managers.

Should the heptavalent botulinum antitoxin be used for botulism type F?

This question is related to clinical management. It should be addressed to clinical and risk managers.

Is ABE antitoxin effective against botulism type F?

The administration of antitoxin as part of the clinical treatment serves to neutralise any unbound toxin and typically does not reverse or relieve existing symptoms [10,34]. The available evidence points towards the lack of effectiveness of bivalent AB antitoxin or trivalent ABE antitoxins for the treatment of type F botulism. In several cases recorded of adult type F botulism the administration of AB or ABE antitoxin did not halt the progression of the disease [2-4,14,15,27,31,32,34].

The quality of the evidence available regarding effectiveness of ABE antitoxin against botulism F is limited to experimental studies in animals, human case-reports and observational descriptive studies. Evidence based on studies of effectiveness that included a comparison group (neither observational, nor randomised control studies) is missing.

Is there any evidence of cross neutralisation between antitoxin E and toxin F?

In vivo studies in animal models and reports of mice bioassay showed various degrees of cross-neutralisation BoNT F and antitoxin E [3,4,25,26]. There is very limited clinical evidence of cross-neutralisation between anti-toxin E and BoNT F, and the available records point to a lack of cross-neutralisation between antitoxin E and BoNT F [2,15,27,31,32,34].

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Annex 1. Search strategies

Cochrane library

Date: 11/07/2013

#1 MeSH descriptor: [Botulinum Toxins] explode all trees

Medline (Pubmed)

Botulinum type F and Antitoxins

Date: 11/07/2013

#1 (("Clostridium botulinum type F"[Mesh] OR "F botulism"[tiab] OR "botulinum toxin type F"[tiab] OR "botulinum toxin f"[tiab] OR "BONT F"[tiab] OR "BONT type F"[tiab] OR "f bont"[tiab] OR "BoNT serotype F"[tiab] OR "BoNTF"[tiab] OR "botulinum neurotoxin F"[tiab] OR "botulinum neurotoxin serotype F"[tiab] OR "Clostridium botulinum F toxin"[tiab] OR "Clostridium botulinum toxin F"[tiab] OR "clostridium botulinum type f toxin"[tiab] OR "BoNT/F"[tiab] OR (botulinum[tiab] OR clostridium[tiab] OR botulism[tiab] OR bont[tiab]) AND F[tiab])) AND (antitoxin*[tiab] OR "Botulinum antiserum"[tiab] OR "Botulinum Antitoxin"[Mesh] OR "Antitoxins"[Mesh])

#2 ("Botulism"[Mesh] OR botulism[tiab] OR "Botulinum Toxins"[Mesh] OR "Botulinum Toxins"[tiab] OR "Botulinum Toxin"[tiab]) AND ("heptavalent botulinum antitoxin"[tiab] OR H-BAT[tiab] OR HBAT[tiab] OR BAT[tiab]))

#3 #1 OR #2

Botulinum type F epidemiological aspects

Date: 12/07/2013

#1 "Epidemiology"[Mesh] OR "epidemiology" [Subheading] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR epidemiology[tiab] OR incidence[tiab] OR prevalence[tiab] OR severity[tiab] OR "Mortality"[Mesh] OR mortality[tiab] OR "death rate"[tiab] OR "death rates"[tiab] OR "case fatality"[tiab] OR "Morbidity"[Mesh] OR morbidity[tiab] OR frequency[tiab] OR occurrence[tiab]

#2 "Clostridium botulinum type F"[Mesh] OR "F botulism"[tiab] OR "botulinum toxin type F"[tiab] OR "botulinum toxin f"[tiab] OR "BONT F"[tiab] OR "BONT type F"[tiab] OR "f bont"[tiab] OR "BoNT serotype F"[tiab] OR "BoNTF"[tiab] OR "botulinum neurotoxin F"[tiab] OR "botulinum neurotoxin serotype F"[tiab] OR "Clostridium botulinum F toxin"[tiab] OR "Clostridium botulinum toxin F"[tiab] OR "clostridium botulinum type f toxin"[tiab] OR "BoNT/F"[tiab]

#3 #1 AND #2

Embase

Botulinum type F and Antitoxins

Date: 11/07/2013

#1 'botulinum toxin f'/exp OR 'f botulism':ab,ti OR 'botulinum toxin type f':ab,ti OR 'botulinum toxin f':ab,ti OR 'bont f':ab,ti OR 'bont type f':ab,ti OR 'f bont':ab,ti OR 'bont serotype f':ab,ti OR 'bontf':ab,ti OR 'botulinum neurotoxin f':ab,ti OR 'botulinum neurotoxin serotype f':ab,ti OR 'clostridium botulinum f toxin':ab,ti OR 'clostridium botulinum toxin f':ab,ti OR 'clostridium botulinum type f toxin':ab,ti OR 'bont/f':ab,ti

#2 ((botulinum OR clostridium OR botulism OR bont) NEAR/2 'f'):ab,ti

#3 #1 OR #2

#4 antitoxin*:ab,ti OR 'botulinum antiserum'/exp OR 'antitoxin'/exp OR 'botulinum antiserum':ti,ab

#5 #3 AND #4

#6 ('botulism'/exp OR botulism:ab,ti OR 'botulinum toxin'/exp OR 'botulinum toxin':ab,ti OR 'botulinum toxins':ab,ti) AND ('heptavalent botulinum antitoxin' OR 'h bat':ab,ti OR hbat:ab,ti OR bat:ab,ti)

#7 #5 OR #6

Botulinum type F epidemiological aspects

Date: 12/07/2013

#1 'botulinum toxin f'/exp OR 'f botulism':ab,ti OR 'botulinum toxin type f':ab,ti OR 'botulinum toxin f':ab,ti OR 'bont f':ab,ti OR 'bont type f':ab,ti OR 'f bont':ab,ti OR 'bont serotype f':ab,ti OR 'bontf':ab,ti OR 'botulinum neurotoxin f':ab,ti OR 'botulinum neurotoxin serotype f':ab,ti OR 'clostridium botulinum f toxin':ab,ti OR 'clostridium botulinum toxin f':ab,ti OR 'clostridium botulinum type f toxin':ab,ti OR 'bont/f':ab,ti

#2 ((botulinum OR clostridium OR botulism OR bont) NEAR/2 'f'):ab,ti

#3 #1 OR #2

#4 'epidemiology'/exp OR epidemiology:ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR 'disease severity'/exp OR severity:ab,ti OR 'mortality'/exp OR mortality:ab,ti OR 'death rate':ab,ti OR 'death rates':ab,ti OR 'case fatality':ab,ti OR 'morbidity'/exp OR morbidity:ab,ti OR frequency:ab,ti OR occurrence:ti,ab

#5 #3 AND #4