



Health Protection Agency Centre for Infections

Duty Doctor Botulism Protocol

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Botulinum Antitoxins from different producers have differing compositions and dosages.

- **Always check with the issuing centre which type is being issued and read the product information sheet for dosages and administration**
- **Ensure the product information sheet accompanies the antitoxin, for use by the hospital doctors caring for the patient**

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For laboratory advice: Dr Kathie Grant
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Requests for Botulinum Antitoxin: Guidance for Duty Doctors

1. Background

These guidelines are for duty doctors dealing with duty calls and they concentrate on advice to be given to clinicians *caring* for a probable (based on clinical diagnosis) case of botulism. They are not intended for giving advice on the clinical management of cases; a responsibility that rests with the attending clinician. Key duty doctor actions in response to a suspected case of botulism are summarised in figure 1.

2. Introduction

Botulinum neurotoxins are produced by the anaerobic spore forming bacterium *Clostridium botulinum* and, rarely by *Clostridium baratii* and *Clostridium butyricum*. There are seven neurotoxins (A-G). Illness in humans is usually caused by types A or B or E, or rarely by F. Types C, D and E cause illness in mammals, birds and fish. Type G has not been shown to be associated with disease.

All toxins block the release of acetylcholine at the neuromuscular junction, which results in flaccid paralysis.

3. Clinical presentation and routes of transmission

There are three naturally occurring forms of botulism:

- **Food-borne botulism**
- **Wound botulism**
- **Infant botulism**

3.1. Food-borne botulism is caused by ingestion of pre-formed toxin in food. Usually occurs after ingestion of foods stored in airtight (i.e. anaerobic) containers – such as canned foods, homemade pickles. Very rarely, intestinal colonisation similar to infant botulism occurs in adults, usually with an underlying reason, such as gastrointestinal abnormalities.

3.2. Wound botulism occurs when anaerobic conditions in a wound contaminated with *Clostridium botulinum* (*C. botulinum*) are created and toxin is formed. Injecting drug users (skin and muscle poppers) are at risk of developing wound botulism.

3.3. Infant botulism occurs following colonisation of the gut with *C. botulinum* with subsequent toxin production. Infants (usually <6 months old) present with very

non-specific effects, such as weakness, hypotonia, hyporeflexia, bulbar palsies, constipation, poor feeding, dehydration. Disease progression in children can be very rapid.

3.4. There is also a further possibility that botulism may occur as a result of deliberate release or as accidental exposure following miss-injection of therapeutic neurotoxin. A deliberate release may involve airborne dissemination of toxin, producing botulism through inhalation. Alternatively, it may involve contamination of food and water supplies either with toxin or with *C. botulinum* bacteria.

3.5. Clinical presentation

In adults irrespective of the route of transmission, characteristically there is bilateral cranial nerve impairment and descending flaccid paralysis. Blurred or double vision, dysphagia and a dry mouth are often the first complaints. These symptoms may extend to a symmetrical flaccid paralysis in a paradoxically alert patient. Fever is usually absent but may occur with concurrent infection. If onset is very rapid there may be no symptoms before sudden respiratory paralysis occurs. In foodborne or intestinal colonisation, vomiting and diarrhoea, followed by constipation precede neurological symptoms.

In infants signs are often non-specific with constipation presenting first, followed by irritability, lethargy, poor feeding, drooling, hypotonia and general weakness. This may progress to descending symmetrical weakness and respiratory failure is a major complication.

4. Management of botulism

- **Early administration of botulinum antitoxin (if indicated)**
- **Search for and debride any wound no matter how trivial**
- **Give antibiotics if wound present**
- **Supportive treatment**

Administration of antitoxin in food-borne and wound botulism is life-saving and must be expedited. Botulinum toxin binds irreversibly to motor end-plates and the aim of antitoxin administration is to block that binding process.

For infant botulism a human derived Botulinum immune Globulin BabyBIG[®] is available from the Infant Botulism Treatment and Prevention Program (IBTPP) California USA (510) 231-7600 <http://www.infantbotulism.org/>. Use of BabyBIG[®] significantly reduces the length of hospital stay and associated hospital costs in

patients with infant botulism. Supportive treatment must also be provided and, although paralysis may persist for several weeks, recovery may be expected.

In wound botulism management of the wounds is also important. All wounds, no matter how trivial should be surgically debrided and treatment with antibiotics (penicillin and metronidazole) should be continued until the wounds have healed completely. Sometimes lesions are not apparent and the presence of deep-seated abscesses or sinuses should be considered.

5. Clinical investigations

Laboratory tests include detection of neurotoxin in clinical and food samples, detection of the organism and isolation from clinical and food samples.

The specimens required depend on the clinical presentation and include:

Foodborne botulism	Wound botulism	Infant botulism
10 ml serum taken prior to antitoxin treatment	10 ml serum taken prior to antitoxin treatment	Serum is not a useful specimen for confirmation of infant botulism
Faeces ^a (10g) or high rectal wash out and 1g inoculated into Cooked Meat Broth or other anaerobic medium	Pus from wound/abscess or debrided tissue in Cooked Meat Broth or other anaerobic medium	Faeces ^a or rectal wash out ^b in Cooked Meat Broth or other anaerobic medium
Vomit, gastric contents, intestinal contents if available		Vomit, gastric contents, intestinal contents if available
Food items implicated (10g)		Food items implicated e.g honey, formula milk

^afaeces may be difficult to obtain due to constipation

^bsee <http://www.infantbotulism.org/> for information on how to perform this procedure in infants

HPA Colindale provides a rapid diagnostic PCR assay for clinical specimens inoculated into CMB

5.1 Routine laboratory tests are NOT helpful.

For food and infant botulism, clinical and food specimens must be forwarded to the HPA Colindale Foodborne Pathogens Reference Unit (FBPRU), immediately. During out of office hours, senior staff of FBPRU must be informed via the out of hours Colindale duty doctor: 0208 200 4400

5.2 Wound botulism

Clinical specimens may not have the same public health urgency and will usually not need to be immediately tested if arriving out of hours.

It is important to note that **botulism is a clinical diagnosis**, which can be confirmed, but not refuted, by laboratory investigations. In cases of food poisoning, toxin is

present in serum or faeces in >50% of cases within one day of onset, but <25% after 3 days. *C. botulinum* will be present in the faeces of >70% of cases within 2 days and 40% 10 days after onset of food poisoning.

For cases of wound botulism the diagnosis is confirmed by the detection of toxin and/or isolation of organism in 41% of cases.

6. Requests for antitoxin

Antitoxin is held at 32 sites around the country and at the HPA Colindale. **The antitoxin is accessible by contacting the duty doctor at Colindale: 0208 200 4400.**

6.1 Upon receipt of a request for antitoxin the duty doctor should:

- Record patient details and those of the clinician making the request, including the level of suspicion (i.e. **where in the list of differential diagnoses does botulism occur**). A botulism questionnaire has been developed on which these details can be recorded. If IDU related the IDU team in Colindale is responsible for sending the questionnaire to the CCDC or the clinical team and for collating the data from the returned completed questionnaires.
- Ensure that the clinical team has informed the CCDC and Consultant Microbiologist locally. **Food-borne botulism is a public health emergency, which must be reported to the CCDC IMMEDIATELY.**
- Ensure that appropriate clinical specimens have been taken **prior** to administration of antitoxin (detailed above in section 5).

6.2 Further advice

If duty doctors need further advice on issue or administration of antitoxin, or want to refer clinicians for medical advice, they may contact Tim Brooks(Porton Down) , Barbara Bannister (Royal Free Hospital) or Nick Beeching (Royal Liverpool University Hospital).

Contact details:

<u>Dr Barbara Bannister</u>	Work:	0207 941 1823/1826
	Mobile:	07831 865912
<u>Dr Tim Brooks</u>	Work:	01980 612774
	Home:	01980 612032
	Mobile:	07766 775149

6.4 Technical data and information on antitoxins

The technical data and information of the Novartis Berhing and MoD Botulinum Antitoxin are found in the duty doctor pack for Botulinum.

Details on the presentation, composition, dosage and administration of the available antitoxins are found in table 1 but should be read in conjunction with the product information leaflet and generic advice below. Technical data and information on BabyBIG[®] can be found on the IBTPP website.

6.4.1 Composition

Antitoxins held in the UK for food and wound botulism are immune serum of F(ab)₂ immunoglobulin fragments sourced from animals. BabyBIG[®] is immune globulin derived from plasma of donors immunised with pentavalent (ABCDE) botulinum toxoid.

6.4.2 Indications

Botulinum Antitoxin is for **Emergency Use Only** for administration to individuals on the slightest suspicion of botulism. Under no circumstances should the treatment be delayed whilst waiting for the results of laboratory investigations and clinical observations.

BabyBIG[®] is indicated for the treatment of patients below one year of age with botulism A and B and has also been used in the USA to treat infant botulism caused by type E.

6.4.3 Administration

Advice on administration is detailed in the product information leaflet which accompanies the antitoxin and this should be followed. Botulinum antitoxins are generally given parenterally by slow intravenous infusion.

Vital signs (pulse, blood pressure and temperature) should be monitored following administration and appropriate medication for the management of acute allergic reactions (hydrocortisone, antihistamine and adrenaline) should be readily available.

For infant botulism information on administration is provided on the IBTPP website.

Novartis Berhing and MoD botulinum Antitoxin preparations do not have a product licence and should only be administered on prescription of a Medical Officer.

BabyBIG® is the only antitoxin licensed for the treatment of infant botulism. The use of Novartis Behring equine antitoxin is not recommended for infant botulism due to the risk of adverse reaction and at present there is insufficient clinical evidence to support the use of MoD ovine antitoxin for treatment of infant botulism.

6.4.4 Repeat antitoxin administration

An effective treatment will prevent further progression of symptoms, but will not reverse established paralysis. If the patient continues to deteriorate the dose may be repeated within 24 hours (within 4-6 hours for Novartis Behring antitoxin).

The chances of an allergic reaction are higher following repeated administrations of antitoxin and the patients should be closely observed for signs of anaphylaxis and serum sickness.

A separate issue of antitoxin will be necessary for additional doses of antitoxin for an individual patient

6.4.5 Special warnings and precautions

Since antitoxin is derived from animal immunoglobulin it carries a risk of allergic reactions such as anaphylaxis and serum sickness. The recipient should therefore remain under medical supervision for 24 hours following administration of the immune serum.

As with all products prepared from biological sources, the transmission of infective agents, including those of unknown origin, cannot be excluded.

Pregnancy and lactation are not contraindications for treatment with Botulism Antitoxin as the indication is a life-threatening condition. However, clinicians should note that no reproduction studies have been carried out on antitoxins so they should only be used if clearly required.

Any effect on the ability to drive and use machines is not known.

Table 1 Botulinum Antitoxin products summary (see product information leaflet for full details)

Manufacturer	Preparation	Composition	Dosage	Administration	Shelf life and storage
Novartis Behring	Horse plasma proteins in 250ml bottle	Per ml: 750iu Anti Type A toxin 500iu Anti Type B toxin 50iu Anti Type E toxin	Adults and children: 500ml as 2 x 250ml bottles, infused whilst observing circulatory effects	Slow iv injection Repeat administration 4-6 hours later with 250ml if clinically indicated (see product information)	Storage at +2 and +8°C and not used after the expiry date on the pack. Open contents should be used immediately
Scottish National Blood Transfusion Service / MoD	Vial of 800mg freeze dried sheep plasma proteins	Per vial: 570iu Anti Type A toxin 3800iu AntiType Btoxin 115iu Anti Type C toxin 120iu AntiType D toxin 305iu Anti Type E toxin 340iu Anti Type F toxin 45iu Anti Type G toxin	Adults and children: 1 vial	Reconstitute vial with 10ml of water for injections at room temperature. By gentle agitation (not shaking). Reconstituted contents of one vial should be administered as a single 10ml slow iv injection over 1-2 mins NB im injection only for mass casualties as causes considerable pain at injection site Repeat administration with further vials if clinically indicated (see product information)	5 year shelf life when stored between +2 and +25 °C Reconstituted contents should be used immediately

Figure 1 Flow chart for dealing with a case of suspect botulism