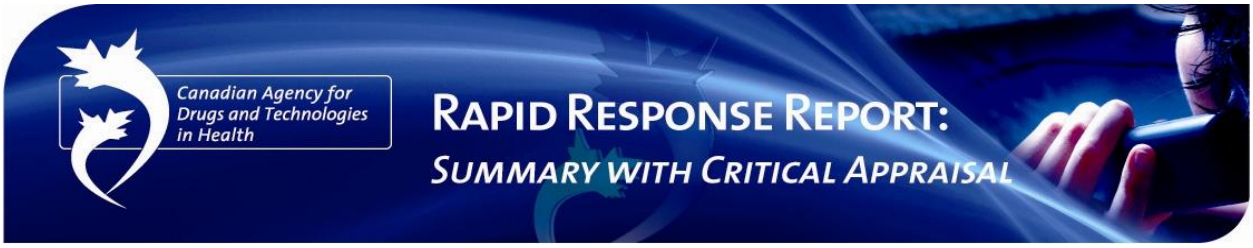


TITLE: Botulinum Antitoxin for the Treatment of Botulism: A Review of the Clinical and Cost-Effectiveness

DATE: 31 October 2012

CONTEXT AND POLICY ISSUES

Botulism is a rare neuroparalytic syndrome caused by neurotoxins produced by the bacterium *Clostridium botulinum*.[1] Botulinum toxin is the most lethal naturally occurring toxin known to exist and may be used as a deadly agent for bioterrorism.[1,2] Botulism occurs in different forms characterized by the mode of acquisition: foodborne botulism, from ingestion of food contaminated with preformed botulinum toxin; infant and adult infectious botulism, from colonization of the host's gastrointestinal tract by *C. botulinum* and in vivo production of toxin; wound botulism, from infection of a wound by *C. botulinum* and in vivo production of toxin; inhalation botulism, from aerosolized toxin.[1,3]

Symptoms of botulism appear within several hours to a few days after initial exposure and may include symmetrical flaccid paralysis, muscle weakness, urinary retention, respiratory failure, and eventually death.[1,3] Paralysis from botulism can last as long as seven months and symptoms of nerve dysfunction may last for more than one year.[1] Botulism diagnosis may be confirmed by demonstrating the presence of toxin in patient specimens using cultures or a mouse bioassay.[1]

There are seven antigenic types of neurotoxins produced by *Clostridium botulinum* that are similar in structure but immunologically distinct.[1] These different serotypes are designated by the letters A through G, and human botulism is cause primarily by serotypes A, B, and E.[1] Standard treatment for botulism includes antitoxin therapy and supportive care, which often includes mechanical ventilation in case of respiratory failure.[1] Antitoxin cannot neutralize toxin once it has bonded to nerve receptors, but it is able to prevent progression of paralysis and is most effective when administered within 24 hours of symptom onset.[1] There are a variety of botulinum antitoxins available, including trivalent equine botulinum antitoxin (for serotypes A, B, and E) and heptavalent equine botulism antitoxin (for serotypes A through G).[3,4]

The purpose of this review is to examine the clinical and cost effectiveness of trivalent and heptavalent botulinum antitoxin for the treatment of botulism.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of trivalent botulinum antitoxin for treatment of botulism?

2. What is the cost-effectiveness of trivalent botulinum antitoxin for treatment of botulism?

3. What is the clinical effectiveness of heptavalent botulinum antitoxin for treatment of botulism?

4. What is the cost-effectiveness of heptavalent botulinum antitoxin for treatment of botulism?

KEY MESSAGE

No relevant information was identified regarding the clinical and cost effectiveness of trivalent and heptavalent botulinum antitoxin for the treatment of botulism.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, The Cochrane Library (2012, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and October 4, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (of any age) with botulism
Intervention	Botulinum antitoxin: Trivalent [A,B,E] or Heptavalent [A,B,C,D,E,F,G]
Comparator	No antitoxin, placebo
Outcomes	Health outcomes, percentage change in health outcomes, length of effect, number of treatments for control of symptoms, disability adjusted life years (DALYs), cost effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, and economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, were duplicate publications or included in a selected systematic review, were published prior to 2002, or were narrative reviews.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[5] A numeric score was not calculated for each study. Instead, strengths and weaknesses of each study were summarized and described. No RCTs, non-randomized studies, or economic evaluations were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 158 citations. Upon screening titles and abstracts, 150 citations were excluded and eight potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were identified through grey literature searching. Of the eight potentially relevant reports, seven did not meet the inclusion criteria. One publication was included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One systematic review met inclusion criteria. No health technology assessments, randomized controlled trials, non-randomized studies, or economic evaluations were selected for inclusion.

Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

Details on study characteristics, critical appraisal and findings can be found in Appendices 3, 4 and 5, respectively.

One systematic review from Canada included patients that were diagnosed with botulism with laboratory confirmation.[6] Inclusion criteria was limited to RCTs and quasi-RCTs of botulism patients treated with trivalent botulism antitoxin, human derived botulinum immune globulin, plasma exchange 3,4-diaminopyridine, and guanidine with standard supportive treatment. The primary outcome was in-hospital mortality from any cause. Secondary outcomes included duration of hospitalization, duration of mechanical ventilation, duration of tube or parenteral feeding, and the risk of adverse events.

Summary of Critical Appraisal

The systematic review was based on a comprehensive literature search and the scientific quality of included studies were assessed and described in detail.[6] Unpublished studies were searched and duplicate study selection and data extraction was performed. Publication bias was not assessed.

Summary of Findings

Clinical effectiveness of trivalent and heptavalent botulinum antitoxin

The systematic did not identify any RCTs that used equine-derived trivalent botulinum antitoxin for the treatment of laboratory-confirmed botulism.[6]

No evidence was identified regarding the use of heptavalent botulinum antitoxin for the treatment of botulism.

Cost effectiveness of trivalent and heptavalent botulinum antitoxin

No evidence was identified regarding the cost effectiveness of trivalent and heptavalent botulinum antitoxin.

Limitations

No relevant information was identified regarding the clinical and cost effectiveness of trivalent and heptavalent botulinum antitoxin for the treatment of botulism. In the included systematic review, the selection criteria were limited to RCTs and quasi-RCTs, which may not have captured all of the relevant studies on botulinum antitoxins as RCTs would be difficult to conduct in an ethical manner. However, both retrospective and prospective observational studies were considered for the current report, and no additional relevant information identified, suggesting a lack of study in this area. Additional studies of potential interest (Appendix 2) were case studies that are neither controlled nor generalizable due to the specific nature of the circumstances and presentations. No cost-effectiveness analyses were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No relevant information was identified regarding the clinical and cost effectiveness of trivalent and heptavalent botulinum antitoxin for the treatment of botulism. One systematic review that was well-conducted and published in 2011 found no RCTs or quasi-RCTs that used trivalent botulinum antitoxin for the treatment of botulism. This suggests a lack of controlled studies on the use of these antitoxins, which may be due to the rarity of the disease.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Dembek ZF, Smith LA, Rusnak JM. Botulism: cause, effects, diagnosis, clinical and laboratory identification, and treatment modalities. Disaster Med Public Health Prep. 2007 Nov;1(2):122-34.

2. Robinson RF, Nahata MC. Management of botulism. Ann Pharmacother. 2003 Jan;37(1):127-31.

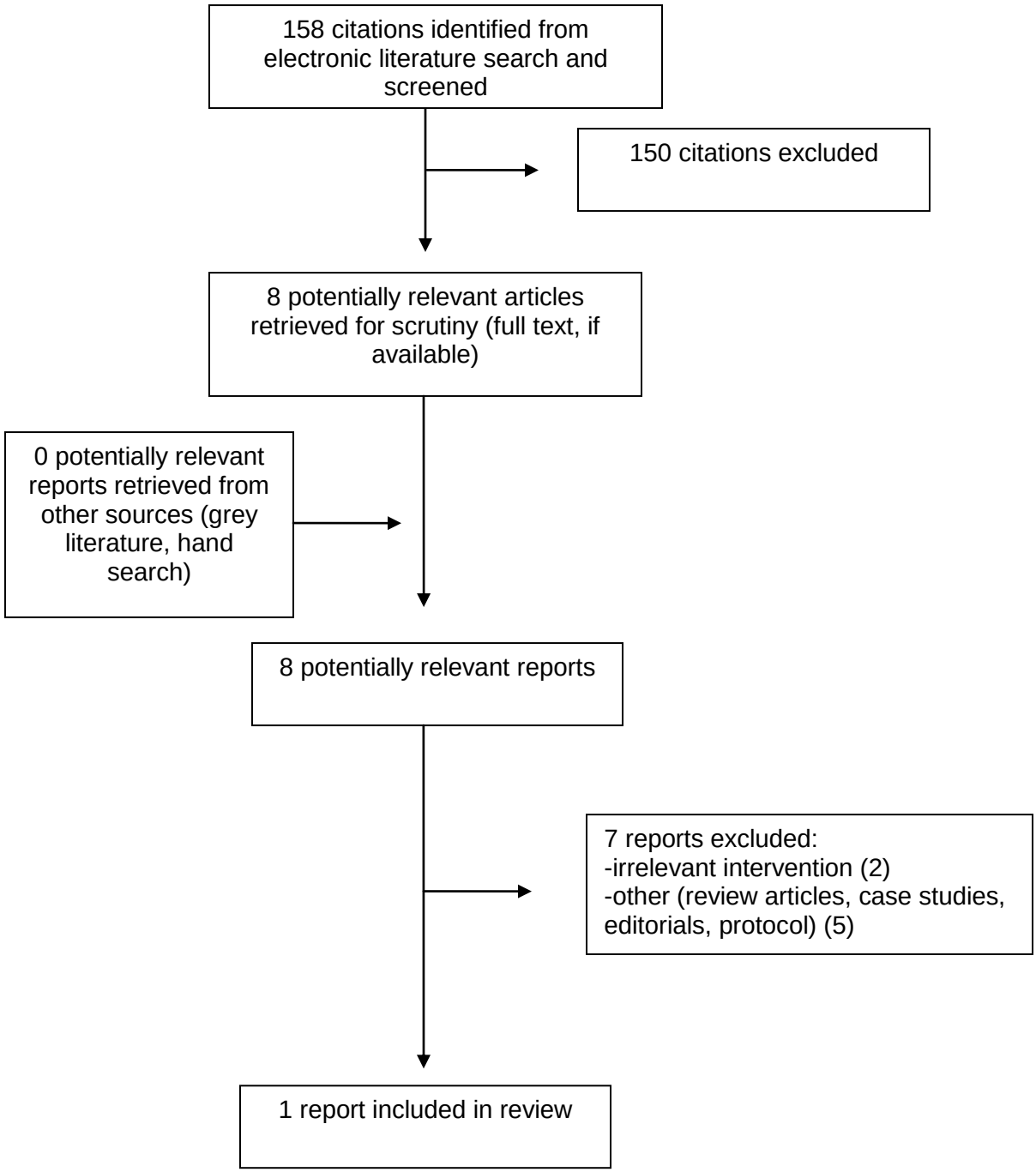
3. Pegram PS, Stone SM. Botulism. 2012 Jun 26 [cited 2012 Oct 17]. In: UpToDate [Internet]. Version 20.9. Waltham (MA): UpToDate, Inc.; 1992 - . Available from: www.uptodate.com Subscription required.

4. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA. 2006 Mar 1;295(9):1023-32.

5. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2012 Jul 30];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

6. Chalk C, Benstead TJ, Keezer M. Medical treatment for botulism. Cochrane Database Syst Rev. 2011;(3):CD008123.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Case studies – trivalent botulinum antitoxin

Lonati D, Locatelli CA, Fenicia L, Anniballi F, Landri P, Giampreti A, et al. Fatal course of foodborne botulism in an eight-month old infant. Pediatr Rep [Internet]. 2011 Sep 30[cited 2012 Sep 30];3(4):e31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283199
PubMed: PM22355516

Oriot C, D'Aranda E, Castanier M, Glaizal M, Galy C, Faivre A, et al. One collective case of type A foodborne botulism in Corsica. Clin Toxicol (Phila). 2011 Oct;49(8):752-4.
PubMed: PM21970773

Pavlova V, Ilieva D, Komitova R, Dimitrova D, Marina M. Outbreak of foodborne botulism in Bulgaria. Problems of Infectious and Parasitic Diseases. 2007;35(2):7-8.

Reller ME, Douce RW, Maslanka SE, Torres DS, Manock SR, Sobel J. Wound botulism acquired in the Amazonian rain forest of Ecuador. Am J Trop Med Hyg. 2006 Apr;74(4):628-31.
PubMed: PM16606997

Zanon P, Pattis P, Pittscheider W, Roscia G, De Giorgi G, Sacco G, et al. Two cases of foodborne botulism with home-preserved asparagus. Anasthesiol Intensivmed Notfallmed Schmerzther. 2006 Mar;41(3):156-9.
PubMed: PM16557441

Case series – trivalent botulinum antitoxin

Varma JK, Katsitadze G, Moiscrafishvili M, Zardiashvili T, Chokheli M, Tarkhashvili N, et al. Signs and symptoms predictive of death in patients with foodborne botulism--Republic of Georgia, 1980-2002. Clin Infect Dis. 2004 Aug 1;39(3):357-62.
PubMed: PM15307002

Chang GY, Ganguly G. Early antitoxin treatment in wound botulism results in better outcome. Eur Neurol. 2003;49(3):151-3.
PubMed: PM12646758

Case studies – heptavalent botulinum antitoxin

Fagan RP, Neil KP, Sasich R, Luquez C, Asaad H, Maslanka S, et al. Initial recovery and rebound of type f intestinal colonization botulism after administration of investigational heptavalent botulinum antitoxin. Clin Infect Dis. 2011 Nov;53(9):e125-e128.
PubMed: PM21896700

APPENDIX 3: Study Characteristics

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Systematic Review					
Chalk[6] 2011 Canada	Systematic Review	Inclusion criteria: Patients with botulism diagnosed by laboratory data	Inclusion criteria: RCTs or quasi-RCTs of diagnosed botulism patients treated with trivalent botulism antitoxin, human-derived, plasma exchange, 3,4-diaminopyridine, and guanidine with supportive treatment.	Placebo	In-hospital mortality, duration of hospitalization, duration of mechanical ventilation/ feeding

APPENDIX 4: Summary of Critical Appraisal

First Author, Publication Year, Study Design	Strengths	Limitations
Systematic Review		
Chalk[6] 2011	• Comprehensive literature search based on pre-defined criteria • Summary of study characteristics and list of included and excluded studies provided • Scientific quality and risk of bias of included studies assessed and documented	• Risk of publication bias not assessed

APPENDIX 5: Summary of Findings

First Author, Publication Year, Study Design	Main Study Findings	Authors' Conclusions
Systematic Review		
Chalk[6] 2011	No RCTs or quasi-RCTs were identified regarding the use of trivalent botulinum antitoxin. One double-blinded, non-crossover RCT was identified that compared the use of human derived botulism immune globulin (n=65) versus control treatment (n=64) for infant botulism. No deaths in treatment or control group. No significant differenes in the risk of adverse events between the two groups. Duration of mechanical ventilation was significantly shorter in treatment group (1.80 weeks; 95% CI 1.20-2.40) compared to control group (4.40 weeks; 95% CI 3.00-5.80). Duration of hospitalization was significantly shorter in treatment group (mean 2.60 weeks; 95% CI 1.95-3.25) compared to control group (5.70 weeks; 95% CI 4.40-7.00).	"There was a single RCT providing evidence for the use of BIG in infant botulism. This study was of high methodological quality. It demonstrated that the use of BIG resulted in significant decreases in the duration of hospitalization, mechanical ventilation and tube or parenteral feeding. There was no significant increase in the risk of adverse events…Although equine derived botulinum antitoxin is considered "standard of care" by many clinicians in the treatment of food-borne botulism, there is no RCT-grade evidence to support its use." (p. 8)