

Pediatric Botulism and Use of Equine Botulinum Antitoxin in Children: A Systematic Review

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Background. Botulism manifests with cranial nerve palsies and flaccid paralysis in children and adults. Botulism must be rapidly identified and treated; however, clinical presentation and treatment outcomes of noninfant botulism in children are not well described.

Methods. We searched 12 databases for peer-reviewed and non-peer-reviewed reports with primary data on botulism in children (persons <18 years of age) or botulinum antitoxin administration to children. Reports underwent title and abstract screening and full text review. For each case, patient demographic, clinical, and outcome data were abstracted.

Results. Of 7065 reports identified, 184 met inclusion criteria and described 360 pediatric botulism cases (79% confirmed, 21% probable) that occurred during 1929–2015 in 34 countries. Fifty-three percent were male; age ranged from 4 months to 17 years (median, 10 years). The most commonly reported signs and symptoms were dysphagia (53%), dysarthria (39%), and generalized weakness (37%). Inpatient length of stay ranged from 1 to 425 days (median, 24 days); 14% of cases required intensive care unit admission; 25% reported mechanical ventilation. Eighty-three (23%) children died. Median interval from illness onset to death was 1 day (range, 0–260 days). Among patients who received antitoxin ($n = 193$), 23 (12%) reported an adverse event, including rash, fever, serum sickness, and anaphylaxis. Relative risk of death among patients treated with antitoxin compared with patients not treated with antitoxin was 0.24 (95% confidence interval, .14–.40; $P < .0001$).

Conclusions. Dysphagia and dysarthria were the most commonly reported cranial nerve symptoms in children with botulism; generalized weakness was described more than paralysis. Children who received antitoxin had better survival; serious adverse events were rare. Most deaths occurred early in the clinical course; therefore, botulism in children should be identified and treated rapidly.

Keywords. botulism; pediatrics; botulinum antitoxin; child, bioterrorism.

Botulism is a potentially fatal neuromuscular disorder caused by botulinum toxin, produced by *Clostridium botulinum* or related species [1]. Botulism can be categorized by mode of transmission and toxin production into several types—foodborne, wound, infant, noninfant intestinal, and iatrogenic—with varied levels of epidemic potential. Foodborne botulism is caused by ingestion of preformed toxin in food; outbreaks occur periodically [2]. Wound botulism is caused by colonization of a wound by *C. botulinum* with in situ toxin production; it has low epidemic potential. Infant botulism is caused by colonization of the immature infant intestine by *C. botulinum* and subsequent toxin production; it is a sporadic disease without epidemic potential that occurs in individuals aged <1 year. It is important to note that infants (<1 year of age) are also susceptible to foodborne botulism. Both noninfant intestinal botulism, also due to intestinal colonization and toxin production, and iatrogenic botulism, systemic paralytic

symptoms in patients injected with botulinum toxin for therapeutic or cosmetic effect, are rare and without epidemic potential.

Botulinum toxin, of which 7 serotypes (designated by letters A–G) have been identified, causes a descending paralysis by irreversibly blocking the release of acetylcholine at the neuromuscular junction. Botulinum toxin has been part of state-sponsored biological weapons programs, and both the toxin and bacteria capable of producing it are classified as select agents subject to federal regulations (42 CFR Part 73) [3, 4]. Because of its severity and outbreak potential through the foodborne route, a single case of botulism is considered a public health emergency [5, 6].

Botulism is characterized by cranial nerve palsies followed by descending flaccid paralysis [7]. Respiratory compromise and death may result from paralysis of the diaphragm, accessory respiratory muscles, or muscles that maintain upper airway patency, unless mechanical ventilation is initiated [4]. In foodborne botulism, nerve palsies may be preceded by acute gastrointestinal symptoms. The rate and extent of paralysis progression varies and is likely dose dependent [5]. Paralysis generally resolves in weeks to months [5].

Traditional laboratory testing for botulism uses a toxin neutralization bioassay for clinical or food specimens in mice, and

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may take up to 10 days. Polymerase chain reaction (PCR) assay and enzyme-linked immunosorbent assay (ELISA) are available to detect botulinum toxin in clinical specimens, and the organism can be cultured; however, these tests also take several days to complete. Therefore, the key therapeutic intervention in botulism, rapid administration of antitoxin, in almost all cases is undertaken based on clinical diagnosis alone [8, 9].

Rapid antitoxin administration and meticulous intensive care, including respiratory monitoring, mechanical ventilation, and nutritional support when required, are the cornerstones of botulism treatment [7–9]. Various equine-derived antitoxin preparations have been available in the past. In the United States, the currently available antitoxin is a heptavalent preparation that contains antibodies against 7 types of botulinum toxin. Antitoxin neutralizes circulating toxin but does not reverse paralysis; therefore, heptavalent antitoxin should be administered as soon as the diagnosis is suspected, and supportive care is required until pretreatment deficits have resolved [8]. Equine antitoxin administration may result in adverse events, including anaphylaxis during first or subsequent doses [10]. Infant botulism is treated with low-titer human-derived antitoxin licensed in the United States for treatment of infant botulism types A and B [11].

Foodborne botulism or wound botulism can affect persons of any age, but most cases occur in adults; the clinical presentation, diagnosis, and response to treatment of botulism in children are not well described. The purpose of this systematic review is to determine what signs and symptoms are of diagnostic value in children with botulism and to describe the effect of botulinum antitoxin administration in children. Additional detail on the use and efficacy of botulinum antitoxin in children may be found in the articles by O'Horo et al and Yu et al in this supplement [12, 13].

METHODS

Protocol and Registration

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (<http://www.prisma-statement.org/>) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; number CRD42015024804).

Eligibility Criteria

Analytic studies, case reports, and case series with primary data on botulism in children (persons aged <18 years) or on administration of equine botulinum antitoxin to children were considered for inclusion. The Council of State and Territorial Epidemiologists 2011 case definitions for botulism were utilized for case classification (<https://wwwn.cdc.gov/nndss/conditions/botulism/case-definition/2011/>). A confirmed case of botulism was defined as a clinically compatible illness with laboratory confirmation, as reported by the authors. For foodborne botulism, a confirmed case was also defined as a clinically

compatible illness in a person who ate the same implicated food as a person with a laboratory-confirmed case. Wound botulism was defined as a clinically compatible illness in a person with a recent open wound or injection drug use. Probable cases utilized the same definitions, but without laboratory confirmation.

Reports were eligible for inclusion if published in peer-reviewed or non-peer-reviewed (eg, *Morbidity and Mortality Weekly Report*) journals in any language from any year. Reports were excluded if they did not include primary data on botulism or antitoxin use in children, did not provide case-specific information, or if they described therapeutic botulinum toxin use not resulting in systemic intoxication. Infant botulism reports were included only if equine antitoxin was administered to the infant. All studies and reports were systematically evaluated to identify the disease course and outcomes, and use and adverse events of equine antitoxin in children. Primary outcomes of the review included morbidity, mortality, length of hospital stay, duration of ventilator dependence, and serious adverse events from botulinum antitoxin.

Information Sources and Searches

A Centers for Disease Control and Prevention (CDC) reference librarian searched Medline (1946 through 20 May 2015), Embase (1988 through 20 May 2015), Embase Dialog (1947–1988), Global Health (1910 through 20 May 2015), the Cumulative Index to Nursing and Allied Health Literature (1980 through 20 May 2015), Cochrane Library (1800 through 20 May 2015), ClinicalTrials.gov (all trials indexed as of 20 May 2015), Scopus (1960 through 20 May 2015), National Technical Information Service, Defense Technical Information Center (DTIC) and government documents via WorldCat, and DTIC documents via Google Scholar. Search terms focused on botulism, botulinum antitoxin, and pediatrics. Additionally, reference lists of relevant reports were hand-searched and botulism subject matter experts were consulted. The full search strategy may be accessed here: http://www.crd.york.ac.uk/PROSPEROFILES/24804_STRATEGY_20150623.pdf.

Study Selection

Two independent reviewers screened search results by title and abstract. Discordant decisions were discussed and adjudicated. Reports that passed initial screening underwent full text review by 2 independent reviewers to assess eligibility. Discordant decisions were discussed and adjudicated (Figure 1).

Non-English article title and abstract screening was done by linguistically proficient individuals or by Google Translate (<https://translate.google.com/>). Reports included in the full text review were professionally translated into English.

Data Collection and Quality Assessment

A data abstraction tool was developed in Epi Info 7 and included checklists for assessing bias and study quality, including a modified US Preventive Services Task Force (USPSTF) Hierarchy

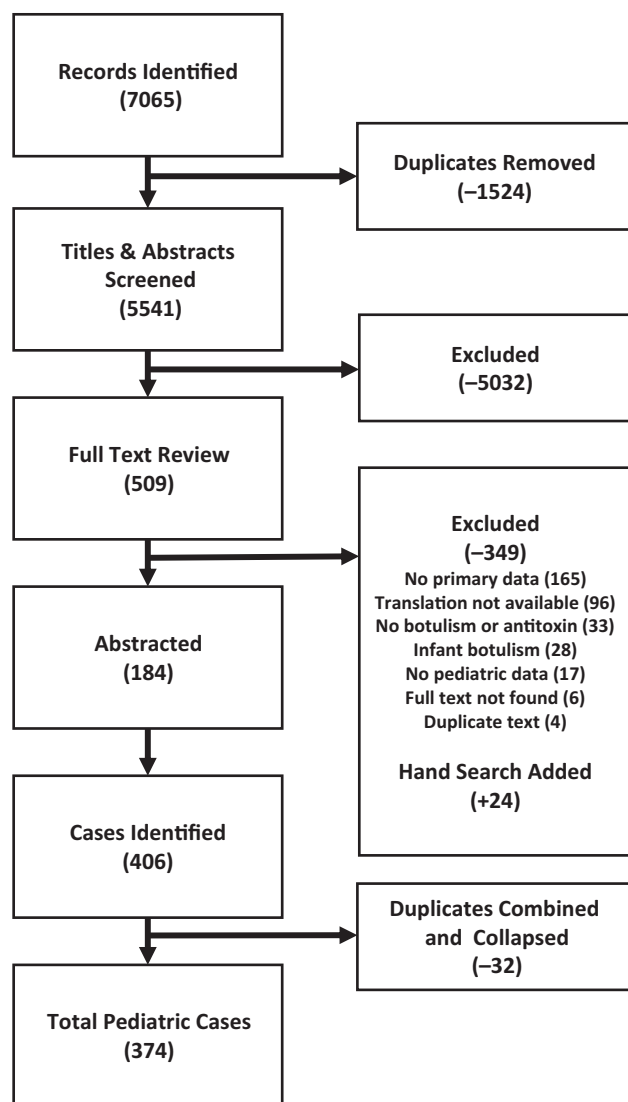


Figure 1. Study selection and case identification.

of Evidence Category Grade to assess study design, a modified Newcastle-Ottawa Scale (NOS) to assess level of certainty and risk of bias, and a data completeness score [14, 15]. Two clinicians abstracted data and assessed the quality of the studies included. Abstracted data included patient demographic information, toxin serotype, transmission type (eg, foodborne), clinical signs and symptoms, diagnostics and imaging, level of care provided, interventions, antitoxin type and dose, adverse events, and patient outcomes.

Data Synthesis and Analysis

Data were extracted from Epi Info 7 into Microsoft Excel for cleaning and de-duplication. Analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, North Carolina). A 1-way analysis of variance was calculated for disease progression and hospitalization trends across age groups. The χ^2 test and relative risk were used to assess outcomes; Mantel-Haenszel

χ^2 test was utilized to assess outcomes by age group, due to small sample sizes. Statistical significance was set at $\alpha = .05$.

RESULTS

Study Selection and Case Identification

A total of 7065 reports were identified through literature review ($n = 7036$) and expert recommendation ($n = 29$). Duplicate reports were removed ($n = 1524$); remaining reports underwent title and abstract screening for eligibility. Full text review was performed on 509 reports; 349 were excluded and 24 new reports were identified from references. A total of 184 reports met inclusion criteria. Each case described in a report was abstracted separately; 406 cases were identified (Table 1). Duplicate cases were identified and combined ($n = 32$), for a total of 374 unique pediatric cases (Figure 1).

Data Quality

All included reports were category III (case reports or case series) in the USPSTF Hierarchy of Evidence for study design, the lowest level of internal validity. On the 0–12 modified NOS for certainty and risk of bias, the median score was 6 (range, 0–10); 12 represents highest quality. Data completeness scores assessed the presence of 15 elements and were categorized as detailed and precise (13–15), somewhat detailed (9–12), or cursory (1–8); the median score was 9 (range, 2–14).

Case Description

Of the 374 pediatric cases of botulism or treatment of botulism, 311 (83%) were foodborne botulism, 30 (8%) wound botulism, 8 (2%) noninfant intestinal botulism, 5 (1%) iatrogenic botulism, 1 (<1%) “other” botulism type, and 7 (2%) unspecified type. Two cases were reported as both foodborne and intestinal. Three (<1%) infant botulism cases and 11 (3%) nonbotulism cases received equine antitoxin and were included for antitoxin-related analyses only. Consequently, 360 pediatric botulism cases and 193 cases receiving antitoxin treatment were included for analysis.

Demographics

Among 360 pediatric botulism cases, 331 (92%) had information on gender; 174 (53%) were male and 157 (47%) female. Ages, available for 342 (95%) patients, ranged from 4 months to 17 years (median and mean, 10 years). Cases were categorized into the following age groups: <1 year of age ($n = 3$ [1%]), 1 year to <5 years ($n = 38$ [11%]), 5 years to <10 years ($n = 116$ [34%]), 10 years to <15 years ($n = 127$ [37%]), and 15 years to <18 years ($n = 58$ [17%]). Cases were reported from 34 countries. Within the United States, 122 cases were reported from 28 states; 2 cases within the United States did not specify a state. Publication years ranged from 1929 to 2015, with median and mean years of 1974 and 1977, respectively (Table 2; Figure 2). Comorbid conditions were reported in 1% of cases.

Table 1. Study Citations

No.	Citation	No. of Pediatric Cases ^a
1	Adorján T, Farkas M, Boros L, Czeglédi Z. [Botulism. Summary based on 6 cases.] <i>Orv Hetil</i> 1998; 139:2495–500.	1
2	Agarwal AK, Goel A, Kohli A, Rohtagi A, Kumar R. Food-borne botulism. <i>J Assoc Physicians India</i> 2004; 52:677–8.	1
3	Aianian KM, Pluzian IA. [Outbreaks of botulism poisoning in the Armenian SSR.] <i>Zh Eksp Klin Med</i> 1967; 7:102–6. In Russian.	3
4	Aianian KM. [On the question of immunity to botulism among people.] <i>Zh Mikrobiol Epidemiol Immunobiol</i> 1967; 44:62–5. In Russian.	4
5	Akdeniz H, Buzgan T, Tekin M, Karsen H, Karahocagil MK. An outbreak of botulism in a family in Eastern Anatolia associated with eating süzme yoghurt buried under soil. <i>Scand J Infect Dis</i> 2007; 39:108–14.	3
6	Alpert G, Campos JM. Wound Botulism in a fourteen-year-old child. <i>Clin Microbiol Newsl</i> 1983; 5:120–1.	1
7	Anlar O, Irmak H, Tombul T, et al. Food-borne botulism cases in Van region in eastern Turkey: importance of electromyography in the diagnosis. <i>Electromyogr Clin Neurophysiol</i> 2003; 43:373–6.	8
8	Argelich R, Nogué-Xarau S, Soler-Abel X, Juan-Serra N. [A family outbreak of foodborne botulism.] <i>Med Clin (Barc)</i> 2014; 142:137–8. In Spanish.	1
9	Armada M, Love S, Barrett E, Monroe J, Peery D, Sobel J. Foodborne botulism in a six-month-old infant caused by home-canned baby food. <i>Ann Emerg Med</i> 2003; 42:226–9. [Erratum appears in <i>Ann Emerg Med</i> 2003; 42:600]	1
10	Atabek ME, Yavuz H, Oran B, Karaaslan S, Erkul I. Plasmapheresis as an adjunct treatment in severe botulism. <i>Intensive Care Med</i> 2002; 28:814.	1
11	Audet D, Landry Y, Gauvreau L, Petrow S, Kasatiya SS, Johnston MA. [Type E botulism. 2 epidemics at Fort Chimo.] <i>Union Med Can</i> 1973; 103:1726–37. In French.	3
12	Aureli P, Di Cunto M, Maffei A, De Chiara G, Franciosa G, Accorinti L, Gambardella AM, Greco D. An outbreak in Italy of botulism associated with a dessert made with mascarpone cream cheese. <i>Eur J Epidemiol</i> 2000; 16:913–8.	6
13	Barboza MM, Santos NF, Sousa OV. [Familiar outbreak of botulism at Ceará state, Brazil: case report.] <i>Rev Soc Bras Med Trop</i> 2011; 44:400–2. In Portuguese.	2
14	Barrett DH, Eisenberg MS, Bender TR, Burks JM, Hatheway CL, Dowell VR Jr. Type A and type B botulism in the North: first reported cases due to toxin other than type E in Alaskan Inuit. <i>Can Med Assoc J</i> 1977; 117:483–9.	2
15	Bauman VM, Yagodinskii VN, Filipovich YV. Clinical and epidemiological characteristics of an outbreak of botulism due to eating of preserved flounder. <i>Zh Mikrob Epid I Immunobiol</i> 1962; 7:92–5.	3
16	Beauvais P, Bouveret JP, Morin M. B botulism. Report of one case. <i>Semaine des Hopitaux</i> 1976; 52:2161–4.	1
17	Beghè R, Centurelli G, Tugnoli F. [Characteristics and present problems of botulism (remarks on an outbreak of familial poisoning).] <i>Policlinico Prat</i> 1967; 74:1149–68. In Italian.	2
18	Bergman R, Insulander S, Lindblad Y. A serologically verified epidemic of botulism in Stockholm involving five members of a family. <i>Acta Medica Scandinavica</i> 1935; 84:496–516.	3
19	Bernasconi C, Nadal D, Wüst J, Lips U, Boltshauser E. Food-borne botulism: an uncommon disorder. <i>Helv Paediatr Acta</i> 1989; 43:515–9.	1
20	Berndt SF. [Botulism.] <i>Med Klin</i> 1978; 73:779–87. In German.	1
21	Beseler-Soto B, Sánchez-Palomares M, Santos-Serrano L, Landa-Rivera L, Sanantonio-Valdearcos F, Paricio-Talayero JM. [Iatrogenic botulism: a complication to be taken into account in the treatment of child spasticity.] <i>Rev Neurol</i> 2003; 37:444–6. In Spanish.	1
22	Blumberger KJ, Gross H. Infection with <i>Cl. botulinum</i> . <i>Deutsche Medizinische Wochenschrift</i> 1936; 62:1451–5.	1
23	Boselli L, Jato E, Selenati A, Sottili S, Bozza Marrubini M. Three cases of severe botulism. <i>Vet Hum Toxicol</i> 1979; 21(Suppl):111–2.	1
24	Bouletreau P, Ducluzeau R, Monier P, Bertrand JL, Bertoye A, Roche L. [Apropos of 17 recent cases of botulism.] <i>Lyon Med</i> 1967; 217:1547–57. In French.	6
25	Brocklehurst JC. Fatal outbreak of botulism among Labrador Eskimos. <i>Br Med J</i> 1957; 2:924.	2
26	Browning LM, Premph H, Little C, Houston C, Grant K, Cowden JM; United Kingdom Botulism Incident Management Team. An outbreak of food-borne botulism in Scotland, United Kingdom, November 2011. <i>Euro Surveill</i> 2011; 16:20036.	3
27	Carman KB, Yakut A. [A nine-year-old boy with double vision, speech disturbance, fatigue and strength loss of extremities.] <i>Türk Pediatri Arsivi</i> 2010; 45:70–1. In Turkish.	1
28	Caruso G, Brienza A, Labianca O. Electrophysiologic and muscle histochemical findings in a case of human botulism. <i>Acta Neurologica (Napoli)</i> 1971; 26:23–5.	1
29	CDC. Botulism—Alaska. <i>MMWR Morb Mortal Wkly Rep</i> 1976; 23:355–6.	1
30	CDC. Botulism associated with commercially canned chili sauce—Texas and Indiana, July 2007. <i>MMWR Morb Mortal Wkly Rep</i> 2007; 56:767–8.	2
31	CDC. Botulism from fresh foods—California. <i>MMWR Morb Mortal Wkly Rep</i> 1985; 34:156–7.	1
32	CDC. Botulism. <i>MMWR Morb Mortal Wkly Rep</i> 1960; 9:2.	2
33	CDC. Botulism—Idaho, Utah. <i>MMWR Morb Mortal Wkly Rep</i> 1974; 23:241–2.	1
34	CDC. Type A botulism associated with commercial pot pie—California. <i>MMWR Morb Mortal Wkly Rep</i> 1977; 26:186–92.	1
35	CDC. Type A botulism from wound infection. <i>MMWR Morb Mortal Wkly Rep</i> 1971; 20:183–4.	1
36	CDC. Wound botulism—Texas, California, Washington. <i>MMWR Morb Mortal Wkly Rep</i> 1980; 29:34–5.	1
37	CDC. Wound botulism. <i>MMWR Morb Mortal Wkly Rep</i> 1971; 20:453.	1
38	CDC. Wound botulism—California. <i>MMWR Morb Mortal Wkly Rep</i> 1974; 23:355–6.	1
39	CDC. Wound botulism—Pennsylvania and Texas. <i>MMWR Morb Mortal Wkly Rep</i> 1974; 23:141–2.	2
40	CDC. Wound botulism—Pennsylvania. <i>MMWR Morb Mortal Wkly Rep</i> 1972; 21:366–7.	1
41	Chaudhry R, Dhawan B, Kumar D, Bhatia R, Gandhi JC, Patel RK, Purohit BC. Outbreak of suspected <i>Clostridium butyricum</i> botulism in India. <i>Emerg Infect Dis</i> 1998; 4:506–7.	5

Table 1. Continued

No.	Citation	No. of Pediatric Cases ^a
42	Cherington M. Botulism. Ten-year experience. Arch Neurol 1974; 30:432–7.	3
43	Cherington M. Botulism: clinical and therapeutic observations. Rocky Mt Med J 1972; 69:55–8.	8
44	Chiorboli E, Fortina G, Bona G. Flaccid paralysis caused by botulinum toxin type B after pesto ingestion. Pediatr Infect Dis J 1997; 16:725–6.	1
45	Christopher JA, Perebrazak CD. Why can't she speak? Pediatr Nurs 2009; 35:203–4.	1
46	Chukhrova VA. [Changes in the electrical activity of the brain in botulism.] Zh Nevropatol Psikhiatr Im S S Korsakova 1970; 70:52–5. In Russian.	1
47	Critchley EM, Hayes PJ, Isaacs PE. Outbreak of botulism in north west England and Wales, June, 1989. Lancet 1989; 2:849–53.	7
48	Crowner BE, Brunstrom JE, Racette BA. Iatrogenic botulism due to therapeutic botulinum toxin a injection in a pediatric patient. Clin Neuropharmacol 2007; 30:310–3.	1
49	D'Agostino L, Semeraro V, Eberlin I. [On 3 cases of botulism in the same family group. Clinical and etiopathogenetic considerations.] G Mal Infett Parassit 1967; 19:961–9. In Italian.	1
50	Date K, Fagan R, Crossland S, Maceachern D, Pyper B, Bokanyi R, Houze Y, Andress E, Tauxe R. Three outbreaks of foodborne botulism caused by unsafe home canning of vegetables—Ohio and Washington, 2008 and 2009. J Food Prot 2011; 74:2090–6.	4
51	Davis JB, Mattman LH, Wiley M. Clostridium botulinum in a fatal wound infection. J Am Med Assoc 1951; 146:646–8.	1
52	de Bisschop G, Dumoulin J, Mouren P. [Electrologic aspect of botulism: 5 cases.] Electrodiagn Ther 1971; 8:57–64. In French.	1
53	de Jesus PV Jr, Slater R, Spitz LK, Penn AS. Neuromuscular physiology of wound botulism. Arch Neurol 1973; 29:425–31.	1
54	Dierksen N, Klutmann G. [Botulism due to clostridium botulinum type D, a germ pathogenic to animals.] Padiatrische Praxis 2009; 73:65–8. In German.	1
55	Dimitrijević J, Deletis V, Grcić N, Milosavljević D. [Botulism. Clinico-electromyographic correlations.] Srp Arh Celok Lek 1984; 112:333–40. In Serbian.	1
56	Dolman CE, Kerr DE. Botulism in Canada, with report of a type E outbreak at Nanaimo, BC. Can J Public Health 1947; 38:48–57.	1
57	Dolman CE. Additional botulism episodes in Canada. Can Med Assoc J 1954; 71:245–9.	1
58	Dolman CE. Human botulism in Canada. Can Med Assoc J. 1953; 68:538–43.	7
59	Dolman CE. Recent observations on type E botulism. Can J Public Health 1957; 48:187–98.	2
60	Engelson G, Johannsen A, Kjellman B. [Botulism caused by Cl. botulinum type E.] Nord Med 1962; 67:339–44. In Swedish.	2
61	Erol S, Kürşat H, Parlak M, Cetin K, Alici HA, Görgün S. An outbreak of food-borne botulism. Eur J Anaesthesiol 1999; 16:500–1.	2
62	Fagan RP, McLaughlin JB, Middaugh JP. Persistence of botulinum toxin in patients' serum: Alaska, 1959–2007. J Infect Dis 2009; 199:1029–31.	2
63	Faich GA, Graebner RW, Sato S. Failure of guanidine therapy in botulism A. N Engl J Med 1971; 285:773–6.	1
64	Faridaalae G, Mohammadi N, Mehryar H, Tabatabaee SJ, Hosseini P, Ahmadi S, Rahmani SH. Botulism poisoning with home canned cheese. Arch Clin Infect Dis 2013; 9(4).	3
65	Fenicia L, Anniballi F, Aureli P. Intestinal toxemia botulism in Italy, 1984–2005. Eur J Clin Microbiol Infect Dis 2007; 26:385–94.	1
66	Fenicia L, Franciosa G, Pourshaban M, Aureli P. Intestinal toxemia botulism in 2 young people, caused by Clostridium butyricum type E. Clin Infect Dis 1999; 29:1381–7.	4
67	Ferreira MS, Nishioka Sde A, de Almeida AB, Silveira PV, de Souza MC, Storti PC, Zenebon O, Gelli DS, de Souza A. [Botulism: considerations about 8 cases occurred in the Triangulo Mineiro, Minas Gerais, Brazil.] Rev Inst Med Trop Sao Paulo 1987; 29:137–41. In Portuguese.	1
68	Figueiredo MA, Dias J, Lucena R. [Comments on two cases of botulism in the State of Bahia, Brazil.] Rev Soc Bras Med Trop 2006; 39:289–91. In Portuguese.	2
69	Figurnov VA, Katin IS. [Botulism cases in the Amur region.] Gig Sanit 2002; 1:66. In Russian.	2
70	Fischer D, Freislederer A, Jorch G. [Sudden death of twins: botulism because of contamination by pap vegetables.] Klin Padiatr 2004; 216:31–5. In German.	2
71	Fleming RH. Report on four cases of botulism in Gatooma, S. Rhodesia. Cent Afr J Med 1960; 6:91–4.	3
72	Frean J, Arntzen L, van den Heever J, Perovic O. Fatal type A botulism in South Africa, 2002. Trans R Soc Trop Med Hyg 2004; 98:290–5.	2
73	Fred HL. Case in point. Wound botulism. Hosp Pract (Off Ed) 1994; 29:39.	1
74	Fullerton P, Gogna NK, Stoddart R. Wound botulism. Med J Aust 1980; 1:662–3.	1
75	Gehrt J. Symptoms and treatment of botulism. Monatsschrift für Kinderheilkunde. 1950; 98:429–31.	5
76	Geiger JC. An outbreak of botulism. JAMA 1941; 117:22.	3
77	Goldstein EM. Safety of high-dose botulinum toxin type A therapy for the treatment of pediatric spasticity. J Child Neurol 2006; 21:189–92.	1
78	Golser A, Plöchl E. [Food-borne botulism in 2 brothers.] Padiatr Padol 1992; 27:21–4. In German.	2
79	Gomá Brufau AR, Vega Romero M, Gallíndez Allende JJ, Hervera Coll G, Vidal Bota J, Sauleda J, Belmonte A. [Botulin toxin poisoning. Involvement of 2 brothers under 7 years of age.] An Esp Padiatr 1987; 26:221–2. In Spanish.	2
80	Gozal Y, Lavi A. [Type E botulism. Weaning from the respirator.] Cah Anesthesiol 1990; 38:35–7. In French.	1
81	Greve-Isdahl F, Holmaas G, Vedeler CA. [Baby with respiratory problems and cardiac arrest.] Tidsskr Nor Laegeforen 2012; 132:429–31. In Norwegian.	1
82	Grizzle CO. Botulism from a puncture wound. Rocky Mt Med J 1972; 69:47–9.	1
83	Hall BL. Botulism from home-canned beets. J Lab Clin Med 1944; 29:702.	2
84	Hall IC. Further outbreaks of botulism in the Rocky Mountain region. Am J Epidemiol 1933; 17:235–51.	7

Table 1. Continued

No.	Citation	No. of Pediatric Cases ^a
85	Hall IC. New outbreaks of botulism in Western United States. <i>J Food Sci</i> 1936; 1:171–98.	19
86	Hansen N, Tolo V. Wound botulism complicating an open fracture. A case report and review of the literature. <i>J Bone Joint Surg Am</i> 1979; 61:312–4.	1
87	Hatanaka T, Owa K, Yasunaga M, Kamezaki S, Suehiro Y, Yasuhara A, Shinomiya K. Electrophysiological studies of a child with presumed botulism. <i>Childs Nerv Syst</i> 2000; 16:84–6.	1
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Table 1. Continued

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Total pediatric cases		406

Abbreviation: CDC, Centers for Disease Control and Prevention.

^aTotal number of cases identified among citations, before duplicate cases discussed in multiple citations were combined and collapsed.

Botulism Characteristics

Of the 360 cases, 283 (79%) were classified as confirmed and 77 (21%) as probable. Reported botulinum toxin serotypes included A (n = 103 [29%]), B (n = 79 [22%]), D (n = 1 [<1%]), E (n = 42 [12%]), not specified (n = 128 [36%]), and multiple types (n = 7 [2%]). Among the 311 foodborne cases, 304 (98%) reported a specific food as the suspected source of botulism, though in most cases it was unclear if toxin was detected in the food. The suspected food was a canned food for 138 (45%) cases, a home canned product for 91 (29%), a meat product (including seafood) for 153 (49%) cases, and a home prepared meat product such as sausage or smoked ham for 54 (17%) cases.

Signs and Symptoms

Several signs and symptoms typical of botulism—cranial nerve palsies and muscle paralysis—were reported in children with botulism; dysphagia was present in more than half the cases and dysarthria, generalized weakness, double vision, and ptosis in more than a third (Table 3). Among cases that reported ptosis, dilated pupils, descending paralysis, or facial drooping, unilateral presentation was noted in a small minority (<6 cases per sign).

Signs and symptoms did not differ with statistical significance between age groups; however, certain findings were notable. Dysphagia was the most commonly reported symptom in each age group, except for cases aged <1 year. The 3 foodborne botulism cases reported in infants were characterized by poor feeding, weak cry, hypotonia, fixed or dilated pupils, constipation, apnea, and lethargy.

Double vision was uncommonly reported among cases aged <5 years; however, it was reported in >30% of cases aged 5 to <18 years, and frequency increased with age.

Dysphagia, dysarthria, and generalized weakness were the 3 most commonly reported signs and symptoms among pediatric botulism cases aged 1 to <10 years. Ptosis, dilated pupils, fixed pupils, and vomiting were also present in >30% of cases in these age groups.

Dysphagia, dysarthria, and double vision were the 3 most commonly reported signs and symptoms among cases aged 10 to <18 years, followed by generalized weakness. Ptosis, dry mouth, and ataxia were also reported for >30% of cases in this age range.

Incubation period could be calculated for 210 (58%) cases. Time from suspected exposure to onset of the first sign or symptom ranged from 0 to 17 days (median, 1 day). Incubation period did not differ by age group ($P = .71$). Progression from

Table 2. Demographics of Pediatric Botulism Cases (N = 360) Identified from a Systematic Review of Literature Published 1929–2015

Characteristic	Frequency		Range			
	No.	%	Minimum	Maximum	Median	Mean
Sex						
Male	174	53%	...	...	...	...
Female	157	47%	...	...	...	...
Age (years)	...	...	0.375	17	10	10
Age group						
<1 y	3	1%	...	...	...	...
1 y to <5 y	38	11%	...	...	...	...
5 y to <10 y	116	32%	...	...	...	...
10 y to <15 y	127	35%	...	...	...	...
15 y to <18 y	58	16%	...	...	...	...
Not specified	18	5%	...	...	...	...
Country^a						
United States	122	34%	...	...	...	...
Italy	26	7%	...	...	...	...
France	22	6%	...	...	...	...
Canada	19	5%	...	...	...	...
Russia	17	5%	...	...	...	...
Germany	16	4%	...	...	...	...
Turkey	16	4%	...	...	...	...
Morocco	12	3%	...	...	...	...
United Kingdom	11	3%	...	...	...	...
Hungary	9	3%	...	...	...	...
India	7	2%	...	...	...	...
Armenia	6	2%	...	...	...	...
Spain	6	2%	...	...	...	...
Country not specified	13	4%	...	...	...	...
State^b (United States)						
Colorado	19	16%				
California	15	12%				
Kentucky	10	8%				
New Mexico	8	7%				
Pennsylvania	8	7%				
Texas	8	7%				
Alaska	7	6%				
Tennessee	6	5%				
Wyoming	5	4%				
Montana	4	3%				
Nebraska	4	3%				
Maryland	3	2%				
Ohio	3	2%				
Washington	3	2%				
State not specified	2	2%				
Publication year	...	...	1929	2015	1974	1977
Case year	...	...	1927	2013	1969	1971

^aCountries with ≤5 cases included Australia, Austria, Brazil, the former Czechoslovakia, Denmark, Greenland, Iran, Israel, Japan, Poland, Portugal, Romania, Senegal, Serbia, South Africa, Sweden, Switzerland, Taiwan, Ukraine, the former Yugoslavia, and Zimbabwe (formerly Rhodesia).

^bStates or territories with ≤2 cases included Alabama, Georgia, Iowa, Idaho, Michigan, Minnesota, Missouri, New Jersey, New York, Oklahoma, Oregon, Puerto Rico, Virginia, and Wisconsin.

onset of first sign or symptom to onset of first neurological sign or symptom could be calculated for 162 (45%) cases. Most cases (n = 133 [82%]) had first neurological sign or symptom onset on the first day of illness; 6 cases had onset ≥4 days later.

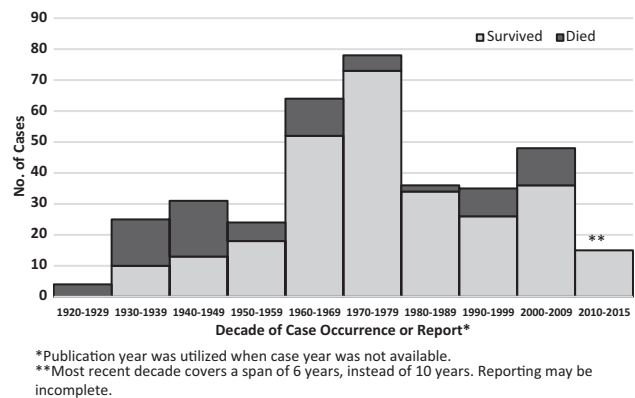


Figure 2. Distribution of pediatric botulism cases from 1920 to 2015, by reported survival status.

Progression from illness onset to first neurological sign or symptom did not differ by age group ($P = .11$).

Differential Diagnoses

A differential diagnosis was reported in 79 (22%) cases; myasthenia gravis (n = 22 [28%]), poisonings and intoxications (n = 45 [25%]), Guillain-Barré syndrome (n = 11 [14%]), and poliomyelitis (n = 9 [11%]) were most commonly listed as alternate diagnoses considered.

Diagnostic Testing and Imaging

Botulism was diagnosed by utilizing the animal bioassay in 255 (71%) cases, culture in 120 (33%) cases, immuno-PCR in 5 (1%) cases, and ELISA in 4 (1%) cases. Some cases were tested by >1 method. Specimen source (clinical or food) was infrequently reported by authors. Among cases for whom a diagnostic test was performed, a positive result was reported for 205 (80%) animal bioassays, 93 (78%) cultures, 5 (100%) immuno-PCR assays, and 2 (50%) ELISAs.

Electromyography (EMG) was conducted in 56 (16%) cases, nerve conduction studies in 16 (4%) cases, and Tensilon tests in 8 (2%) cases. Abnormalities were reported by the authors for 46 cases (82%) who underwent EMG, 6 (36%) who had nerve conduction studies, and none of the 8 who had Tensilon tests.

Additional diagnostic and imaging procedures included the following: Lumbar puncture was documented in 51 (14%) cases, with generally nonspecific findings. Computed tomography and magnetic resonance imaging of brain and spine were performed infrequently (n = 29); abnormal findings (n = 3) were few and nonspecific (mild brain edema, n = 2) or attributed to chronic, underlying conditions (n = 1).

Clinical Course

Medical care was sought for 288 (80%) cases; 54 (19%) of these were seen as outpatients. Among 11 cases for which the number was available, outpatient encounters occurred once per patient

Table 3. Signs and Symptoms by Age Group of Pediatric Botulism Cases Identified From a Systematic Review of Literature Published 1929–2015

System	Signs and Symptoms	All Ages (N = 360)		<1 y (n = 3)		1 to <5 y (n = 38)		5 to <10 y (n = 116)		10 to <15 y (n = 127)		15 to <18 y (n = 58)	
		No.	%	No.	no./No.	No.	%	No.	%	No.	%	No.	%
Constitutional	Dizziness	51	14%	0	...	4	11%	12	10%	15	12%	16	28%
	Fatigue	41	11%	0	...	2	5%	8	7%	19	15%	11	19%
	Fever	36	10%	0	...	4	11%	14	12%	12	9%	4	7%
	Lethargy	24	7%	2	2/3	1	3%	10	9%	5	4%	6	10%
Respiratory	Dyspnea	95	26%	1	1/3	6	16%	32	28%	38	30%	16	28%
	Apnea	37	10%	2	2/3	5	13%	9	8%	17	13%	4	7%
FEN/GI	Dysphagia	191	53%	0	...	17	45%	62	53%	71	56%	32	55%
	Constipation	90	25%	2	2/3	10	26%	27	23%	33	26%	10	17%
	Abdominal pain	86	24%	0	...	4	11%	31	27%	33	26%	14	24%
	Nausea	72	20%	0	...	2	5%	20	17%	29	23%	19	33%
Neurological	Poor feeding	18	5%	3	3/3	4	11%	6	5%	0	...	1	2%
	Dysarthria	141	39%	0	...	12	32%	45	39%	56	44%	27	47%
	Generalized weakness	132	37%	1	1/3	13	34%	46	40%	46	36%	23	40%
	Double vision	125	35%	0	...	4	11%	36	31%	55	43%	29	50%
	Ptosis	121	34%	1	1/3	12	32%	41	35%	45	35%	21	36%
	Dilated pupils	120	33%	2	2/3	12	32%	43	37%	43	34%	16	28%
	Fixed pupils	108	30%	3	3/3	12	32%	38	33%	36	28%	15	26%
	Vomiting	108	30%	0	...	12	32%	38	33%	37	29%	17	29%
	Ophthalmoplegia	104	29%	1	1/3	10	26%	31	27%	36	28%	23	40%
	Dry mouth	103	29%	0	...	8	21%	27	23%	41	32%	21	36%
	Ataxia	98	27%	1	1/3	8	21%	27	23%	40	31%	21	36%
	Blurry vision	87	24%	0	...	2	5%	23	20%	37	29%	21	36%
	Descending paralysis	45	13%	1	1/3	3	8%	14	12%	14	11%	9	16%
	Diminished gag reflex	45	13%	1	1/3	3	8%	12	10%	21	17%	8	14%
	Sore throat	43	12%	0	...	2	5%	17	15%	16	13%	7	12%
	Facial droop	38	11%	1	1/3	2	5%	13	11%	11	9%	7	12%
	Urinary retention	37	10%	0	...	3	8%	15	13%	12	9%	6	10%
	Reduced deep tendon reflexes	31	9%	1	1/3	4	11%	7	6%	13	10%	5	9%
	Hypotonia	26	7%	3	3/3	3	8%	11	9%	7	6%	2	3%
	Dry eyes	18	5%	0	...	2	5%	6	5%	9	7%	1	2%
	Somnulence	14	4%	0	...	3	8%	4	3%	4	3%	3	5%
	Nystagmus	13	4%	0	...	0	...	4	3%	4	3%	5	9%
	Altered mental status	11	3%	0	...	3	8%	3	3%	4	3%	1	2%
	Increased oral secretions	9	3%	0	...	2	5%	3	3%	4	3%	0	...
	Tremors	5	1%	0	...	1	3%	0	...	3	2%	1	2%
	Weak cry	4	1%	3	3/3	0	...	1	1%	0	...	0	...
	Increased lacrimation	1	0%	0	...	1	3%	0	...	0	...	0	...

Abbreviation: FEN/GI, fluids, electrolytes, nutrition, and gastrointestinal.

(8 cases), twice (2 cases), or thrice (1 case). In 6 cases, patients reported receiving outpatient care only, with no inpatient care; 5 (83%) of these children died. Nine additional patients were seen as outpatients, with inpatient care not specified; 7 (78%) of these children died.

For most cases ($n = 270$ [75%]), patients received inpatient care (Figure 3) for a median duration of 24 days (range, 1–425 days). Intensive care unit (ICU) admission was reported for 37 (14%) cases for a median duration of 14 days (range, 1–42 days). Duration of hospitalization ($P = .40$) and ICU stay ($P = .56$) did not differ significantly by age group.

Mechanical ventilation was reported in 91 (25%) cases for a median of 17 days (range, 1–259 days). Tracheostomy was required in 31 (33%) of these cases; in 2 cases tracheostomy was placed in anticipation of mechanical ventilation, which ultimately was not required. Median duration of tracheostomy use was 38 days (range, 8–90 days).

Antitoxin

Botulinum antitoxin was administered to 193 patients: 179 pediatric botulism cases, 3 infant botulism cases, and 11 non-botulism cases. A median of 2 doses (range, 1–9) were given

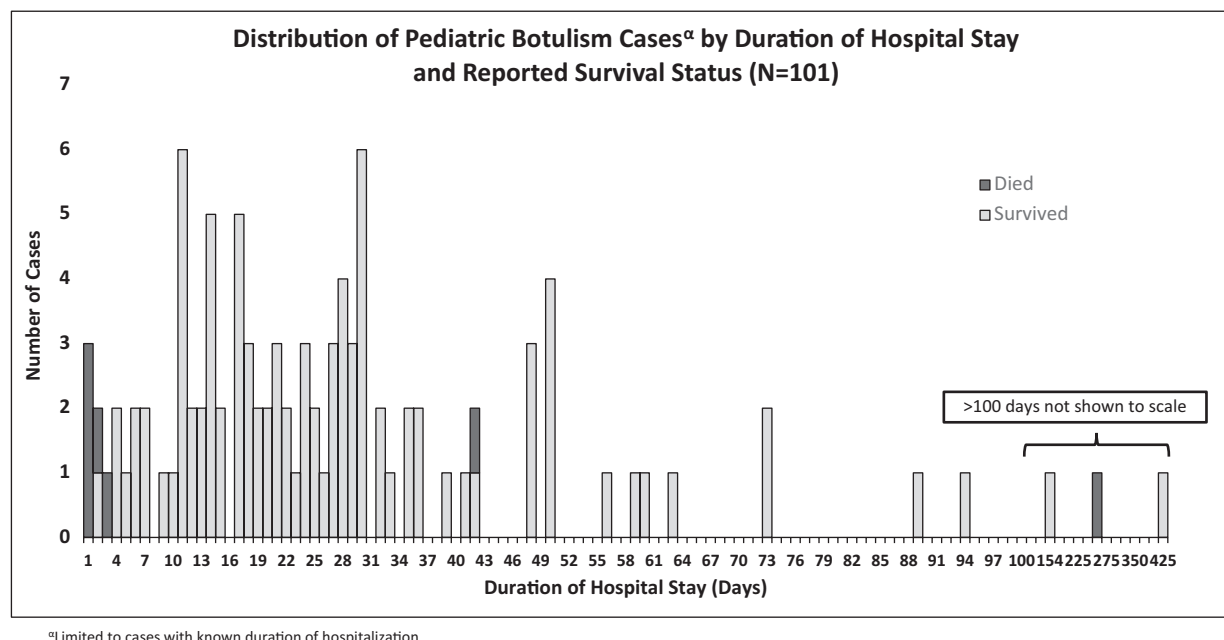


Figure 3. Distribution of pediatric botulism cases, by duration of hospital stay and reported survival status (n = 101).

per patient. Cases were treated with various equine antitoxins as follows: bivalent, 105 (37%); trivalent, 57 (20%); monovalent, 28 (10%); quadrivalent, 12 (4%); and heptavalent, 3 (1%). Six (2%) patients received polyvalent antitoxin not described further. For seventy cases (25%), antitoxin type was not specified.

An adverse event was reported in 23 (12%) pediatric recipients of antitoxin, which included “persistent hypotension and cardiovascular collapse” in 1 child who died, serum sickness in 6 (3%) children, and anaphylaxis in 5 (3%) children. Other adverse events included rash (11 [6%]), fever (7 [4%]), edema (2 [1%]), and pruritus, dyspnea, nausea, and vomiting (1 [$<1\%$] each).

Outcomes

Of 270 hospitalized cases, disposition among those surviving to discharge was specified for 41 (15%); of these, 34 (83%) were discharged home without inpatient or outpatient rehabilitation, and 7 (17%) were discharged to rehabilitation centers.

Of the 360 pediatric botulism patients, 83 (23%) died. Case fatality rates did not vary significantly by age group (Table 4). Case fatality rates varied over time, from a maximum of 22% during 1940–1949 to a minimum of zero during 2010–2015 (Figure 2). Cause of death was classified as due to botulism or primary respiratory failure (n = 35 [42%]), complications of botulism (n = 3 [4%]), administration of antitoxin (n = 1 [1%]), or unrelated to botulism or treatment of botulism (n = 1 [1%]); cause of death in 43 (52%) was not specified.

The time interval from illness onset to death could be calculated for 44 (53%) cases. Median interval was 1 day (range, 0–260 days), and the interval did not differ significantly by age

group ($P = .33$). The time interval from hospital admission to death could be calculated for 23 (28%) cases, with a median of 1 day (range, 0–252 days).

Among the 101 patients for whom duration of inpatient admission was known, 7 died; of these, 5 died in the first 3 days of hospitalization (Figure 3).

Impact of Antitoxin on Outcomes

The relative risk (RR) of death among pediatric botulism cases treated with antitoxin (n = 17 deaths) compared with those not treated with antitoxin (n = 27 deaths) was 0.24 (95% confidence interval [CI], .14–.40; $P < .0001$). When evaluated by age group, patients aged 1 to <5 years (RR, 0.11 [95% CI, .02–.79]; $P = .028$), patients aged 5 to <9 years (RR, 0.16 [95% CI, .06–.44]; $P < .0004$), patients aged 10 to <15 years (RR, 0.20 [95% CI, .06–.65]; $P = .007$), and patients aged 15 to <18 years (RR, 0.19 [95% CI, .04–.99]; $P = .048$) had significantly decreased relative risk of death among those who received antitoxin. The relative risk of patients aged <1 year could not be calculated (Table 4).

DISCUSSION

Our review of botulism in children suggests that pediatric patients’ clinical presentation, clinical course, and response to antitoxin treatment are similar to those described for adult patients, with a few important caveats. Clinicians are most likely to observe dysphagia, dysarthria, and generalized weakness in children with botulism. Signs and symptoms of botulism are similar across childhood age groups; however, recognition of botulism in younger children and infants requires increased

Table 4. Mortality by Age Group and Treatment With Antitoxin Among Pediatric Botulism Cases Identified From a Systematic Review of Literature Published 1929–2015

Age Group	All Cases		Treated With Antitoxin				Not Treated With Antitoxin				Relative Risk		
	Population, No.	Died, No. (%)	Population, No.	Died, No. (%)	Survived, No. (%)	NS	Population, No.	Died, No. (%)	Survived, No. (%)	NS	RR	PValue	95% CI
All ages	360	83 (23)	179	17 (10)	156 (87)	6	66	27 (41)	38 (58)	1 (2)	0.24	<.0001	.14–.40
By age group													
<1 y	3	1 (33)	1	1 (100)	0 (0)	0	2	0 (0)	2 (100)	0 (0)	...	...	...
1 y to <5 y	38	14 (37)	15	1 (7)	14 (93)	0	10	6 (60)	4 (40)	0 (0)	0.11	.0280	.02–.79
5 y to <10 y	116	32 (28)	51	4 (8)	44 (86)	3	21	11 (52)	10 (48)	0 (0)	0.16	.0004	.06–.44
10 y to <15 y	127	23 (18)	66	7 (11)	58 (88)	1	20	6 (30)	13 (65)	1 (5)	0.20	.0071	.06–.65
15 y to <18 y	58	10 (17)	32	2 (6)	29 (91)	1	9	3 (33)	6 (66)	0 (0)	0.19	.0480	.04–.99
Age NS	18	3 (17)	14	2 (14)	11 (79)	1	4	1 (25)	3 (75)	0 (0)	0.62	.6540	.07–5.14

Abbreviations: CI, confidence interval; NS, not specified; RR, relative risk of death among pediatric botulism cases treated with antitoxin compared with those not treated with antitoxin.

reliance on clinical signs (such as ophthalmoplegia) rather than on reported symptoms (such as double vision). Progression of illness can be rapid; when respiratory compromise and death occur, it is often within a day of symptom onset. Children who receive botulinum antitoxin are more likely to survive.

The clinical presentation of botulism is classically described as cranial nerve palsies followed by bilateral descending flaccid paralysis; in children, the most common manifestations in our study were cranial nerve–related dysphagia, dysarthria, and generalized weakness more than paralysis. These signs and symptoms were consistent across age groups, with the corresponding presentation in infants described as poor feeding (potentially a manifestation of dysphagia), weak cry, and hypotonia. Of note, an alert infant with hypotonia, ptosis, and fixed pupils may be mischaracterized as being lethargic. Eye findings, including double vision, ptosis, dilated pupils, and fixed pupils, were also common; however, signs were more common than symptoms in younger children. Younger children may not be able to articulate the symptoms they are experiencing, such as double vision or dry mouth, leading these symptoms to be underreported in younger age groups. Clinicians should recognize that children <10 years of age may present with dysphagia, dysarthria, generalized weakness, ophthalmoplegia, and vomiting, while children aged ≥10 years of age may complain of dysphagia, dysarthria, double vision, generalized weakness, ptosis, and dry mouth. Reported ataxia likely represents weakness or blurry vision, as botulism does not affect the cerebellum.

Progression of illness can be rapid in children with botulism. The incubation period for most cases was 1 day and most deaths occurred within 1 day of illness onset. This highlights the importance of early clinical suspicion for botulism, provision of meticulous intensive care, and administration of botulinum antitoxin as soon as possible. Laboratory testing might subsequently confirm the diagnosis, but treatment should be initiated based on clinical diagnosis.

We found that equine antitoxin administration to children with botulism reduced mortality by 76% and that adverse events associated with antitoxin administration were infrequent and mostly minor. Serious adverse events including serum sickness, anaphylaxis, and cardiovascular collapse leading to 1 death occurred but were relatively rare. We note that antitoxin preparations in this study were reports from over the course of 9 decades in 35 countries and varied in valence, antigenicity, concentration, and neutralizing capacity. We did not seek to determine optimal antitoxin dose or timing of administration. Our findings support current CDC recommendations to administer antitoxin to patients with suspected botulism as soon as possible [16].

Caring for children with botulism can be resource intensive, even when antitoxin is administered early in the course of illness. Children require a high level of care and frequent monitoring. Most cases in our review required inpatient care lasting weeks, and a subset of these required ICU admission. Mechanical ventilation, when required, was prolonged and tracheostomy frequent. It is essential that medical and nursing staff recognize that children with botulism may be alert, despite their inability to move, speak, or breathe and that appropriate psychological support measures be instituted.

This study is subject to at least 3 limitations. First, information collected by this study consisted of author reports in published journals. Reporting standards may have varied by journal, geographic region (35 countries represented), and decade (reports spanned the years 1927–2015). Diagnostic criteria for botulism, including laboratory methods, may also vary by geography and time period. Second, medical care, particularly intensive and critical care, vastly changed over the time period covered by this review; mechanical ventilation entered medical practice halfway through the period covered. The outcomes we describe are averaged over nearly a century. Pediatric mortality over the entire time period of this review was 23%, which is similar to historical fatality rates for adult botulism [17], but different than current all-age mortality from botulism in

the United States which is <3% [18]. Fatality rates in pediatric botulism in the most current time period of our review are in line with the current all-age mortality in the United States. Third, publication bias may have favored cases of botulism with unusual presentation or greater severity. This review does not represent active surveillance data.

Children with botulism are more likely to survive when treated rapidly with botulinum antitoxin. In the United States, a physician suspecting botulism in a child should immediately call the state public health department emergency phone number. The state will connect the physician to CDC's 24-hour Botulism Clinical Consultation Service for a telephone consult by a botulism expert and, when indicated, immediate shipment of botulinum antitoxin from the Strategic National Stockpile to the patient's bedside.

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