Efficacy of Human Botulism Immune Globulin for the Treatment of Infant Botulism: The First 12 Years Post Licensure

Jessica R. Payne, MPH[1], Jessica M. Khouri, MD[1], Nicholas P. Jewell, PhD[2], and Stephen S. Arnon, MD, MPH[1]

Objectives To report the efficacy of Human Botulism Immune Globulin Intravenous (BIG-IV) in the first 12 years following its licensure in 2003 and to characterize its use nationwide in treating patients with infant botulism.

Study design Medical records and billing information were collected for US patients treated with BIG-IV from 2003 to 2015. Length of hospital stay (LOS) and hospital charge information for treated patients were compared with the BIG-IV Pivotal Clinical Trial Placebo Group to quantify decreases in LOS and hospital charges.

Results The use of BIG-IV reduced mean LOS from 5.7 to 2.2 weeks. This shortened hospital stay resulted in a mean decrease in hospital charges of $88 900 per patient. For all US patients 2003-2015, total decreases in LOS and hospital charges were 66.9 years and $86.2 million, respectively. The decrease in mean LOS was time dependent: BIG-IV treatment on hospital days 0-3 reduced mean LOS by 3.7 weeks ($P < .001$ vs the BIG-IV Pivotal Clinical Trial Placebo Group), on hospital days 4-7 by 2.6 weeks ($P < .001$ vs the BIG-IV Pivotal Clinical Trial Placebo Group) and on hospital days 8-10 by just 1 week (P = NS). Since licensure, 1192 patients in 48 states and Washington, DC, have been treated with BIG-IV.

Conclusions The use of BIG-IV since its licensure in 2003 treated approximately 93% of US patients with laboratory-confirmed infant botulism, and prevented >65 years in hospital stay and >$85 million in hospital charges from occurring. The greatest LOS reduction was achieved when BIG-IV was administered soon after hospital admission. Effective and appropriate use of BIG-IV in the US has continued in the postlicensure period. *(J Pediatr 2018;193:172-7).*

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Infant botulism is an acute, life-threatening paralytic infectious disease of infants and is the most common form of human botulism in the US.[1] Infant botulism results when swallowed spores of *Clostridium botulinum* (or rarely, neurotoxigenic *Clostridium baratii* or *Clostridium butyricum*) germinate and produce botulinum neurotoxin in the infant's large intestine. The absorbed toxin is transported by the circulation to the neuromuscular junction, where it blocks release of acetylcholine and causes flaccid paralysis.[2] Botulinum neurotoxin exists in 8 antigenic variants (A-H) that are distinguished by the inability of a polyclonal antitoxin raised against 1 toxin type to neutralize any of the other 7 toxin types in the standard mouse bioassay.[3,4]

Before the development of Human Botulism Immune Globulin Intravenous (BIG-IV), the treatment of patients with infant botulism consisted only of meticulous nutritional and respiratory supportive care.[5] Severely paralyzed patients often were hospitalized for several months before recovering sufficient strength to enable discharge.[6] Before BIG-IV became available, equine-derived immunoglobulin G botulinum antitoxins were not used to treat patients with infant botulism in the US because of safety concerns and their short in vivo half-lives.[7] In 1990-1992, the California Department of Public Health (CDPH) made BIG-IV from hyperimmune plasma donated by volunteers who had been boosted with an investigational (ie, unlicensed) botulinum toxoid. In 1992-1997, the CDPH conducted a phase III pivotal clinical trial of BIG-IV that demonstrated safety and efficacy by reducing the mean hospital stay by 3.1 weeks and mean hospital charges by $88 600 in 2004 US dollars ($112 300 when adjusted into 2015 US dollars).[8] After 6 years of nationwide open-label distribution as an investigational new drug that treated a life-threatening illness and filled an unmet medical need, BIG-IV was licensed by the US Food and Drug Administration (FDA) to CDPH on October 23, 2003, under its proprietary name BabyBIG.[5,8] BIG-IV is a public service (ie, not-for-profit) orphan drug that CDPH provides nationwide in accord with the

BIG-IV	Human Botulism Immune Globulin Intravenous
CDPH	California Department of Public Health
FDA	US Food and Drug Administration
HD	Hospital day, that is, numerical day of hospitalization
LOS	Length of hospital stay
PCTPG	BIG-IV Pivotal Clinical Trial Placebo Group

From the [1]Infant Botulism Treatment and Prevention Program, Infectious Diseases Laboratory Branch, Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health, Richmond; and [2]Division of Biostatistics, School of Public Health, University of California, Berkeley, CA

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federal Orphan Drug Act and state law. BIG-IV is the first and only treatment for infant botulism licensed in the US and, as such, constitutes first-line therapy for infant botulism.

As the US license-holder for BIG-IV, CDPH has continued to monitor its efficacy following licensure as measured by decreases in length of hospital stay (LOS) and in hospital charges.[9] Here we report the use and continued efficacy of BIG-IV throughout the US in its 12 years since licensure. We also report the benefit to efficacy of prompt treatment.

Methods

CDPH produces and distributes this human-derived medicine nationwide as required by the federal Orphan Drug Act and state law. As the sole source of BIG-IV in the world, CDPH knew of all US patients treated with BIG-IV for suspected or laboratory-confirmed infant botulism in the 12 years that followed its licensure in 2003. Demographic information was obtained from medical records at the time of treatment. Information on laboratory-confirmed patients with infant botulism in the US not treated with BIG-IV was gathered from annual Council of State and Territorial Epidemiologists National Botulism Surveillance summaries.[1] All infants treated with BIG-IV had an enema or fecal specimen tested for the presence of botulinum neurotoxin and/or *C botulinum* at an approved laboratory using standard methods to establish the diagnosis of infant botulism and determine toxin type.[3]

This study included all laboratory-confirmed patients with infant botulism in the US with illness caused by botulinum toxin type A or type B, which together accounted for >99% of all infant cases of botulism in the US in the study period. Patients with dual toxin type Ba and type Bf accounted for approximately 1% of the study population and were assigned to the toxin type B illness category.

LOS was defined as the total number of full days the patient was hospitalized. As authorized by federal regulations,[9] to determine admission and discharge dates, discharge summaries were obtained for all hospitalizations related to the patient's illness with infant botulism. For each patient's inpatient stay, itemized hospital bills also were obtained to determine the total charges billed for the hospital stay.[9] Hospital charges were used as a surrogate for the cost of the illness. These charges do not include the fees of the attending physicians, unless these were billed through the hospital, the costs of transferring the patient by ambulance, or indirect costs to parents such as lost work time and hotel bills. The marked-up statutorily-required fee ($45 300) for BIG-IV charged by the hospital to the patient was subtracted from the hospital charges before analysis because this amount varied by several orders of magnitude among hospitals. Using information from the US Bureau of Labor Statistics (https://www.bls.gov/data/) for the San Francisco metropolitan area, the Los Angeles metropolitan area, the New York–New Jersey metropolitan area, and the Philadelphia–New Jersey metropolitan area, all hospital charges were adjusted annually into current-year dollars using the lowest percentage increase in medical costs in the previous year that occurred in 1 of these 4 metropolitan regions. Adjusted hospital charges are reported in 2015 US dollars.

Mean LOS and hospital charges were compared with the 1992-1997 BIG-IV Pivotal Clinical Trial Placebo Group (PCTPG)[8] to quantify reductions in these outcome measures. Total reductions in LOS and hospital charges were calculated for type A and type B illness separately and then summed to obtain the cumulative total.

Hospital day (HD) of treatment was defined as the difference between the date of treatment and the date of hospital admission for the continuous hospitalization during which BIG-IV was given. Before licensure, open-label distribution of BIG-IV demonstrated efficacy only when administered within the first 7 days of hospitalization.[8] For this reason, only infants in the US treated with BIG-IV within the first 7 days of hospital admission were included in the mean and cumulative efficacy calculations. All patients treated with BIG-IV in the US in the study period, regardless of HD of treatment, were included in the calculation of mean LOS and hospital charges by treatment day category.

Statistical Analyses

The 2-sample *t* test was used to compare outcomes (eg, LOS or hospital charges) across treatment and placebo groups. In all such comparisons, the reported *P* values used the more conservative value for tests that (i) assumed equal variances, or (ii) assumed unequal variances. In addition, Kolmogorov-Smirnov exact *P* values were also calculated. The Kolmogorov-Smirnov test examines the similarity of the entire distributions of reported outcomes, whereas the *t* test examines a shift in the mean only. Test of trend was also performed for efficacy variables across all treatment day categories.

Results

In the 12 years that followed FDA licensure of BIG-IV in October 2003, the medicine was administered to 1192 patients with infant botulism in the US. Of these patients, 1133 (95%) received BIG-IV within the first 7 days of hospitalization (**Tables I** and **II**). The mean LOS of these patients was 2.2 weeks ($P = .0001$ vs PCTPG) and their mean hospital charges were $118 600 ($P = .001$ vs PCTPG). The cumulative LOS avoided and cumulative hospital charges avoided by use of BIG-IV for all patients treated within 7 days of hospital admission 2003-2015 were calculated to be 66.9 years and $86 201 700, respectively (**Table I**).

Mean LOS and hospitalization charges differed between patients with illness caused by toxin type A and illness caused by toxin type B (**Table II**). Patients with illness caused by toxin type A had a mean LOS of 2.4 weeks and mean hospital charges of $135 600, and patients with illness caused by toxin type B had a mean LOS of 2.0 weeks and mean hospital charges of $107 000. Compared with PCTPG, type A patients had larger mean LOS reductions (4.3 weeks) and hospital charges savings ($96 400) than the type B patients did (2.2 weeks and $63 400, respectively). Cumulative LOS reductions and hospital charges

Table I. Reductions in hospital stay and charges achieved with BIG-IV treatment of US patients with infant botulism during its pivotal clinical trial and the 12 years after licensure*

Patient cohort	n	Mean stay (wk) ± SE	*P* value†	Hospital stay avoided: Mean stay (wk) ± SE‡	Hospital stay avoided: Total (y)§ ± SE‡
Placebo group for pivotal clinical trial (CA)‖	63	5.7 ± 0.6	—	—	—
Patients with infant botulism treated with BIG-IV during the pivotal clinical trial (CA)	59	2.6 ± 0.3	.0001 (KS < .001)	3.1 ± 0.7	3.5 ± 0.8
Patients with infant botulism treated with BIG-IV in the first 12 years after licensure (US)	1133	2.2 ± 0.04	.0001 (KS < .001)	3.6 ± 0.6	66.9 ± 10.5

	n	Mean charges¶ ± SE	*P* value†	Hospital charges avoided¶: Mean ± SE‡	Hospital charges avoided¶: Total§ ± SE‡
Placebo group for pivotal clinical trial (CA)‖	63	$207 500 ± $25 600	—	—	—
Patients with infant botulism treated with BIG-IV during the pivotal clinical trial (CA)	59	$95 200 ± $15 400	.0003 (KS < .001)	$112 300 ± $29 800	$6 624 600 ± $1 760 500
Patients with infant botulism treated with BIG-IV in the first 12 years after licensure (US)	1123	$118 600 ± $3 500	.001 (KS = .002)	$88 900 ± $25 800	$86 201 700 ± $25 434 300

*Treated with BIG-IV in the US within 7 days of hospital admission. Only patients with type A or type B illness included.
†*P* value for comparison to the placebo group. The first *P* value was determined using the *t* test, the second using the Kolmogorov-Smirnov (KS) test.
‡SE of differences and sums do not assume equal variances in subgroups.
§Totals are calculated separately for patients with types A and B illness and then summed for the cumulative total (see Table II); hence, total (years) is not the product of the n × mean stay avoided (wk).
‖Reference group composed of pivotal clinical trial placebo-treated patients 1992-1997.[8] LOS numbers rounded to 1 significant figure.
¶All charges adjusted to year 2015 dollars and rounded to the nearest $100. LOS data and actual charge data available for >99% of patients; n = number of patients with available data.

savings for the 12-year postlicensure period for type A patients were 38.0 years and $43 839 100, respectively; for type B patients, these metrics were 28.9 years and $42 362 600, respectively (Table II).

Patients treated with BIG-IV on HDs 0-3 had a mean LOS of 2.0 weeks ($P < .0001$ vs PCTPG) and mean hospital charges of $109 100 ($P = .0003$ vs PCTPG), and patients treated on days 4-7 had a mean LOS of 3.1 weeks ($P = .0002$ vs PCTPG) and mean hospital charges of $165 600 ($P = .14$). BIG-IV treatment on HDs 8-10, 11-14, and >15 resulted in increasingly longer mean LOS and greater hospital charges. Compared with patients in the 1992-1997 BIG-IV PCTPG, only treatment categories 0-3 days and 4-7 days had significantly shortened hospital stays and reduced charges (Table III). For treated infants the tests of trend (both linear and logarithmic) for day of initial treatment versus mean stay and mean charges were highly significant ($P < .001$ for all tests).

Of the 59 patients treated >7 days after admission, 24 patients (40.7%) received inpatient care in only one hospital, of which almost three-quarters (17/24, 70.8%) were either specialty children's or academic institutions. Twenty-six additional infants of the 59 patients (44.1%) were cared for in a primary and a referral hospital, of which the first was either a general or community hospital, and of which more than

Table II. Reductions in hospital stay and charges achieved with BIG-IV treatment of US patients with infant botulism 2003-2015, stratified by botulinum toxin type A or B of illness*

Efficacy outcomes		Placebo group for pivotal clinical trial (CA)†	Patients with infant botulism treated with BIG-IV in the first 12 years after licensure (US)	Placebo group for pivotal clinical trial (CA)†	Patients with infant botulism treated with BIG-IV in the first 12 years after licensure (US)
Hospital stay		**Type A illness**		**Type B illness**	
n		38	462	25	671
Mean stay in wk ± SE		6.7 ± 1.0	2.4‡ ± 0.09	4.2 ± 0.4	2.0‡ ± 0.04
Hospital stay avoided	Mean in wk ± SE§	—	4.3 ± 1.0	—	2.2 ± 0.4
	Total in y‖ ± SE§	—	38.0 ± 8.9	—	28.9 ± 5.6
Hospital charges		**Type A illness**		**Type B illness**	
n		38	455	25	668
Mean charges¶ ± SE		$231 900 ± $38 300	$135 600‡ ± $7 100	$170 400 ± $27 200	$107 000‡ ± $3 200
Hospital charges avoided¶	Mean ± SE§	—	$96 400 ± $38 900	—	$63 400 ± $27 300
	Total‖ ± SE§	—	$43 839 100 ± $17 701 900	—	$42 362 600 ± $18 263 300

*Treated with BIG-IV in the US within 7 days of hospital admission. Only patients with type A or type B illness included.
†Reference group comprised of pivotal clinical trial placebo-treated patients 1992-1997.[8] LOS numbers rounded to 1 significant figure.
‡*P* < .001 for the toxin-type-specific mean as compared with the same toxin type mean in the placebo group.
§Standard errors (SE) of differences and sums do not assume equal variances in subgroups.
‖Totals are calculated separately for patients with type A and type B illness and then summed for the cumulative total; hence, total (years) is not the product of the n × mean stay avoided (wk).
¶All charges adjusted to year 2015 dollars and rounded to the nearest $100. LOS data and actual charge data available for >99% of patients; n = number of patients with available data.

Table III. Reductions in hospital stay and charges achieved with BIG-IV treatment of US patients with infant botulism, 2003-2015, stratified by HD of infusion*

Patient cohort	n	Mean hospital stay (wk) ± SE	*P* value†	n	Mean Hospital Charges‡ ± SE	*P* value†
Placebo group for pivotal clinical trial (CA)§	63	5.7 ± 0.6	—	63	$207 500 ± $25 600	—
Patients with infant botulism treated with BIG-IV in the first 12 years after licensure (US)	1192	2.3 ± 0.05	<.0001 (KS < .001)	1182	$131 400 ± $4 500	.005 (KS = .004)
Patients treated on HD 0 to 3	941	2.0 ± 0.04	<.0001 (KS < .001)	935	$109 100 ± $3 400	.0003 (KS < .001)
Patients treated on HD 4 to 7	192	3.1 ± 0.15	.0002 (KS < .001)	188	$165 600 ± $11 800	.14 (KS = 0.35)
Patients treated on HD 8 to 10	31	4.7 ± 0.8	.32 (KS = 0.31)	31	$293 000 ± $74 300	.28 (KS = 0.55)
Patients treated on HD 11 to 14	14	6.7 ± 1.1	.50 (KS = .015)	14	$445 600 ± $123 400	.08 (KS = 0.11)
Patients treated on HD >15	14	6.5 ± 0.9	.58 (KS = .06)	14	$492 400 ± $85 200	.006 (KS < .001)

*Only patients with type A or type B illness included.
†*P* value for comparison with the PCTPG.[8] The first *P* value was determined using the *t* test, the second using the Kolmogorov-Smirnov (KS) test.
§Reference group comprised of pivotal clinical trial placebo-treated patients 1992-1997. LOS numbers rounded to 1 significant figure.
‡All charges adjusted to year 2015 dollars and rounded to the nearest $100. LOS data and actual charge data available for >99% of patients; n = number of patients with available data.

two-thirds (18/26, 69.2%) of the second hospitals were either specialty children's or academic institutions to which the patient had been transferred within 48 hours of admission to the first hospital. Thus, it seems that most (35/59, 59.3%) patients treated late in the disease course were in specialty children's or tertiary academic hospitals within 48 hours of admission, settings generally conducive to the prompt consideration of the diagnosis of infant botulism.

In its 12 years of postlicensure distribution, approximately 93% of all US laboratory-confirmed infant botulism cases were treated with BIG-IV. These patients resided in 48 states and Washington, DC. The remaining 7% of non-BIG-IV-treated, laboratory-confirmed cases resided in 27 states and Washington, DC. Information on LOS and hospital charges could not be obtained for these non-BIG-IV-treated patients. The 10 states, in descending order, with the most cases of infant botulism during the study period were California, Pennsylvania, New Jersey, Maryland, Texas, Utah, New York, Washington, Ohio, and Colorado (**Figure**).

Discussion

In the 12-year period after its licensure, the use of BIG-IV to treat patients with infant botulism in the US with type A or type B illness in the first 7 days of hospitalization reduced mean LOS by 3.6 weeks and the corresponding mean hospital charges by $88 900 per patient. This 3.6-week decrease in mean hospital LOS is greater than the 3.1-week reduction demonstrated in the 1992-1997 BIG-IV pivotal clinical trial.[8] However, as found in that study, treatment with BIG-IV shortened the mean LOS more for patients with type A infant botulism than for patients with type B infant botulism (**Table I**). Both studies used the PCTPG as their comparator.

The total LOS and total hospital charges avoided during the 12-year postlicensure period were 66.9 years and $86.2 million (in 2015 US dollars), respectively (**Table I**). To determine the cost effectiveness of BIG-IV for US patients, the State of California statutorily-required fee for providing BIG-IV was subtracted from the patient's hospital charges before analysis, as was previously done.[8] Hence, the fee charged for BIG-IV did not inflate the charges of the treated group compared with the PCTPG and enabled calculation of the cost-benefit ratio for BIG-IV of 1.96 ($88 900/$45 300).

This report achieved 99.2% ascertainment of LOS and hospital charge information for these postlicensure BIG-IV–treated patients. However, a possible limitation of this study is that the only comparison group available was the placebo-treated cohort of patients in the pivotal clinical trial of BIG-IV 1992-1997. In the years since then, substantial changes have occurred in the way hospital care is administered and charged.[10]

When comparing the efficacy outcome measures for patients treated in 2003-2015 with those treated in 1992 (**Table I**), it might seem that the hospital charge savings achieved through use of BIG-IV has declined despite the further shortening of mean hospital stay in 2003-2015 (2.6 weeks vs 2.2 weeks, respectively). We surmise that this apparent decrease in charge savings achieved with use of BIG-IV reflects the substantial increase in healthcare costs in recent decades. In the 15 years from 1990 to 2014, national healthcare expenditures increased from 12.1% to 17.5% of the gross domestic product,[11] and hospital costs now account for nearly one-third of US healthcare expenses.[12]

However, the magnitude of hospital charges avoided through use of BIG-IV substantially underestimates the total societal cost savings achieved by this medicine. This conclusion results from our study design, which was unable to obtain the costs of attending physician fees, lost parental work time, travel, hotel, and additional child care expenses, as well as ambulance and the occasional aircraft transportation costs for these often critically ill patients. Also, to be conservative in adjusting hospital charges into current year dollars, we used the lowest annual increase that occurred among the 4 reference major metropolitan healthcare markets (the San Francisco metropolitan area, the Los Angeles metropolitan area, the New York–New Jersey metropolitan area, and the Philadelphia–New Jersey metropolitan area; see Methods).

The 1998-2003 nationwide open-label Treatment Investigational New Drug study did not evaluate the efficacy of BIG-IV when given >1 week after hospital admission.[8] In our study,

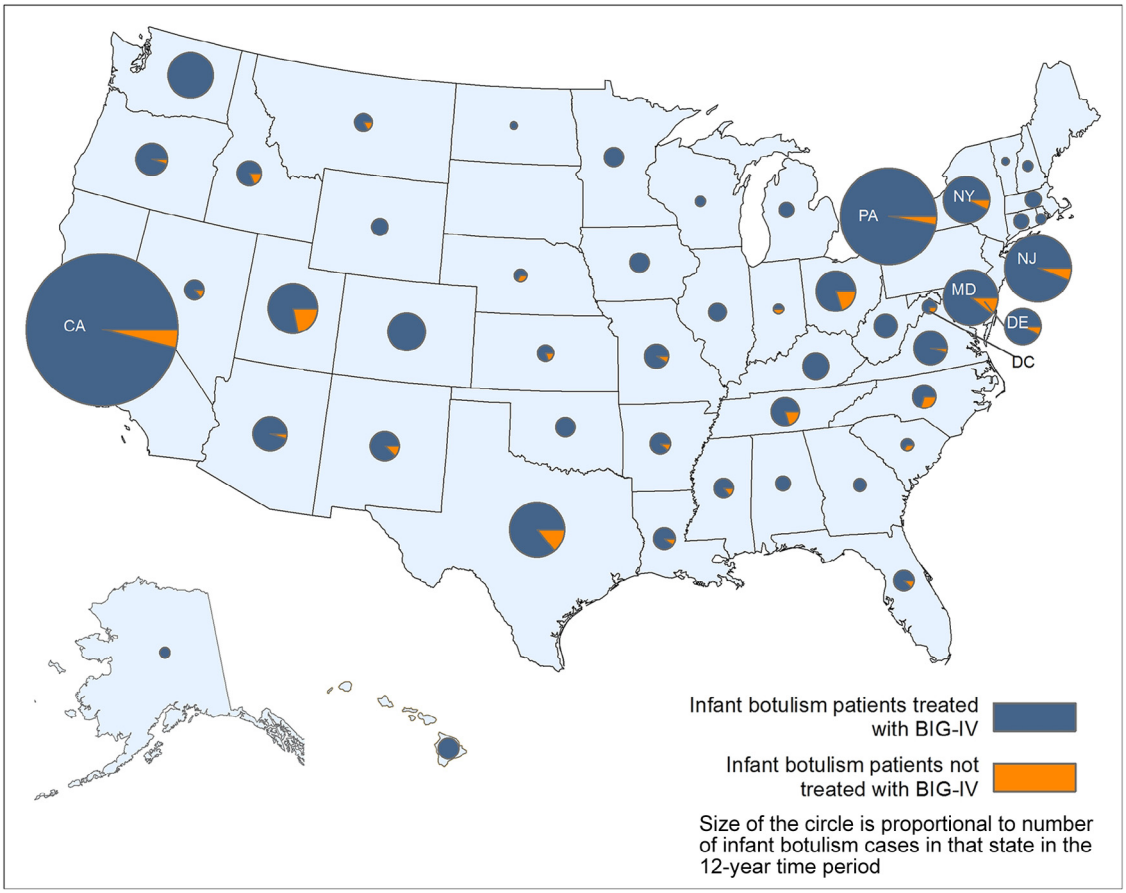

Figure. Use of BIG-IV in the US, 2003-2015. National map with pie charts placed over each state in which laboratory-confirmed infant botulism cases occurred from 2003 to 2015.

59 patients with infant botulism in the US received BIG-IV on HD >7. Accordingly, we categorized US-treated patients by HD of BIG-IV administration and compared mean LOS and mean hospital charges with those of the PCTPG (**Table III**). Patients treated within the first week of hospitalization had a significant 3.6-week decrease in the mean LOS, and patients treated on HDs 8-10 had a 1-week decrease in the mean LOS, which did not achieve statistical significance. Also, patients treated on HD >10 had a mean LOS (>6.5 weeks) that was longer than the mean LOS of the untreated PCTPG comparison group (5.7 weeks) (**Table III**). We were unable to discern from our data whether these late-treated patients had atypical or catastrophic presentations that delayed consideration of the diagnosis of infant botulism[13,14] and, hence, delayed their treatment with BIG-IV. These findings further underscore the need to treat patients with suspected infant botulism promptly with BIG-IV.

A significant linear trend was found between the increasing HD on which BIG-IV was administered and an increase in mean LOS and mean hospital charges. This finding reinforces the importance of prompt clinical recognition of infant botulism and treatment with BIG-IV to hasten recovery and maximally decrease LOS. Although BIG-IV efficacy has not been demonstrated for treatment beyond HD 7, physicians may consider treating at HD >7 if the patient's recovery has plateaued or worsened,[15,16] if toxemia has been demonstrated, or if antibiotic treatment is needed, because starting antibiotics may worsen the symptoms of infant botulism.[13,17] Hospital charges were notably higher for the 59 patients treated at >7 days into their hospital stay (mean charges ≥$293 000; **Table III**), presumably because of preceding extensive and costly diagnostic studies (eg, magnetic resonance imaging, electroencephalography, electromyography, etc) and because of having been hospitalized, often in intensive care, for ≥1 week with ongoing but untreated botulinum toxemia.

A recent report described trends in outcomes and hospitalization charges for patients with infant botulism at 3-year intervals between 1997 and 2009 using samples of patients drawn from the overlapping Kids' Inpatient Database (n = 504) and National Inpatient Sample (n = 340) database.[18] Study patients were identified by use of the *International Classification of Diseases,* 9th edition, discharge diagnosis codes for botulism (all types); laboratory confirmation of diagnosis was not required.[18] Because the report's study population was less than one-half the size of the laboratory-confirmed patients with infant botulism (n = 1192) that comprise our report and

because of other differences in methodologies,[18] the results of the 2 studies cannot be compared accurately. Other analyses that reported improved outcomes with use of BIG-IV[19-21] were based on subsets of patients who were enrolled either in the 1992-1997 statewide pivotal clinical trial or in the 1998-2003 national Treatment Investigational New Drug clinical trial of BIG-IV.[8]

BIG-IV continues to be a highly efficacious and cost-effective orphan drug following licensure. As the only medicine approved for the treatment of infant botulism, BIG-IV is first-line therapy for this illness. The high percentage (93%) of laboratory-confirmed patients with infant botulism in the US who were treated with BIG-IV after licensure indicates widespread use of this public service (ie, not-for-profit) orphan drug. To maximize efficacy of BIG-IV and maximally shorten LOS, early recognition and prompt treatment of suspected patients with infant botulism is essential. Treatment with BIG-IV should not be delayed for laboratory confirmation of diagnosis. Physicians, including non-US physicians,[15,16,22-25] wishing to obtain BIG-IV should contact the Infant Botulism Treatment and Prevention Program of CDPH at +1-510-231-7600; consultation is available 24/7/365. Further information on obtaining BIG-IV and on infant botulism can be found at www.cdph.ca.gov/infantbotulism and www.infantbotulism.org. ■

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Reprint requests: Stephen S. Arnon, MD, MPH, Infant Botulism Treatment and Prevention Program, California Department of Public Health, 850 Marina Bay Pkwy, E-361, Richmond, CA 94804. E-mail: stephen.arnon@cdph.ca.gov

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