

ORIGINAL ARTICLE

# Human Botulism Immune Globulin for the Treatment of Infant Botulism

Stephen S. Arnon, M.D., Robert Schechter, M.D., Susan E. Maslanka, Ph.D.,  
Nicholas P. Jewell, Ph.D., and Charles L. Hatheway, Ph.D.\*

ABSTRACT

From the Infant Botulism Treatment and Prevention Program (S.S.A., R.S.), California Department of Health Services, Richmond; the National Botulism Surveillance and Reference Laboratory, Centers for Disease Control and Prevention, Atlanta (S.E.M., C.L.H.); and the Division of Biostatistics, School of Public Health, University of California, Berkeley (N.P.J.). Address reprint requests to Dr. Arnon at the California Department of Health Services, 850 Marina Bay Pkwy., Rm. E-361, Richmond, CA 94804, or at sarnon@dhs.ca.gov.

\*Deceased.

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## BACKGROUND

We created the orphan drug Human Botulism Immune Globulin Intravenous (BIG-IV), which neutralizes botulinum toxin, and evaluated its safety and efficacy in treating infant botulism, the intestinal-toxemia form of human botulism.

## METHODS

We performed a five-year, randomized, double-blind, placebo-controlled trial statewide, in California, of BIG-IV in 122 infants with suspected (and subsequently laboratory-confirmed) infant botulism (75 caused by type A *Clostridium botulinum* toxin, and 47 by type B toxin); treatment was given within three days after hospital admission. We subsequently performed a 6-year nationwide, open-label study of 382 laboratory-confirmed cases of infant botulism treated within 18 days after hospital admission.

## RESULTS

As compared with the control group in the randomized trial, infants treated with BIG-IV had a reduction in the mean length of the hospital stay, the primary efficacy outcome measure, from 5.7 weeks to 2.6 weeks ( $P<0.001$ ). BIG-IV treatment also reduced the mean duration of intensive care by 3.2 weeks ( $P<0.001$ ), the mean duration of mechanical ventilation by 2.6 weeks ( $P=0.01$ ), the mean duration of tube or intravenous feeding by 6.4 weeks ( $P<0.001$ ), and the mean hospital charges per patient by \$88,600 (in 2004 U.S. dollars;  $P<0.001$ ). There were no serious adverse events attributable to BIG-IV. In the open-label study, infants treated with BIG-IV within seven days of admission had a mean length of hospital stay of 2.2 weeks, and early treatment with BIG-IV shortened the mean length of stay significantly more than did later treatment.

## CONCLUSIONS

Prompt treatment of infant botulism type A or type B with BIG-IV was safe and effective in shortening the length and cost of the hospital stay and the severity of illness.

INFANT BOTULISM, AN ORPHAN DISEASE, IS the most common form of human botulism in the United States<sup>1</sup> and results from an unusual infectious condition termed intestinal toxemia. Swallowed spores of *Clostridium botulinum* (or rarely, neurotoxicogenic *C. butyricum* or *C. baratii*) germinate and temporarily colonize the lumen of the large intestine, where as vegetative cells they produce botulinum neurotoxin.<sup>2,3</sup> The toxin is absorbed and carried by the bloodstream to the neuromuscular junction, where it binds irreversibly.<sup>4,5</sup> The clinical spectrum of laboratory-confirmed cases ranges from mild, outpatient illness to sudden, fatal respiratory arrest, but almost all of the 80 to 110 cases identified in the United States annually are recognized because their severity necessitates hospital admission<sup>6-9</sup> (Fig. 1).

Botulinum toxin is one of the most poisonous substances known<sup>10</sup> and exists in seven antigenic variants (types A to G) that are distinguished by the inability of antitoxin against one type to neutralize any other type; the types of toxin serve as useful clinical and epidemiologic markers. Almost all cases of infant botulism in the United States have resulted from type A or type B toxin.<sup>1,11,12</sup> Historically, untreated patients with infant botulism caused by type A toxin had a mean length of hospital stay that was significantly longer than that of untreated patients with infant botulism caused by type B toxin,<sup>9</sup> and treatment was limited to supportive care.

The equine botulism antitoxin used for adult patients has not been used to treat patients with infant botulism in the United States, because of its serious side effects when given to adults (including serum sickness and anaphylaxis),<sup>13</sup> its short half-life (five to seven days),<sup>14</sup> and its potential for lifelong sensitization to equine proteins. For these reasons, we created Botulism Immune Globulin Intravenous (Human) (BIG-IV), a human-derived botulism antitoxin that neutralizes botulinum toxin. We evaluated its safety and efficacy in a five-year, randomized, double-blind, placebo-controlled clinical trial statewide, in California, and a subsequent six-year nationwide, open-label study.

## METHODS

### PATIENTS AND ELIGIBILITY

The study population for the randomized trial consisted of all infants admitted to hospitals in Cali-



**Figure 1. Three-Month-Old Patient with Mild Infant Botulism.**

Ptosis, an expressionless face, and hypotonia of the neck, trunk, and limbs are evident. The additional bulbar palsies of ophthalmoplegia, weak cry, weak sucking, and dysphagia (drooling) are not apparent in the photograph.

fornia because of suspected botulism from February 24, 1992, to March 24, 1997. The open-label study population consisted of patients who had suspected infant botulism, initially in California and later nationwide, between the end of the randomized trial and licensure of BIG-IV in October 2003. Follow-up observation continued until all patients had been discharged from the hospital after admission for the management of infant botulism and its complications.

Infants were eligible for the trial if they had acute flaccid paralysis consistent with infant botulism according to the history, physical examination, and laboratory findings at admission and had been hospitalized for less than three days (72 hours). This enrollment limitation reflected concern that any efficacy of BIG-IV might decrease over time as motor-nerve intoxication proceeded.

A laboratory-confirmed case of infant botulism was defined as an illness consistent with the

known paralyzing action of botulinum toxin in which *C. botulinum* toxin or organisms were eventually identified in the patient's feces or enema specimen. In both the randomized trial and the open-label study, enrollment was based on bedside clinical diagnosis; in almost all cases, laboratory confirmation of the diagnosis was not obtained until after infusion of the study medication.

Potential subjects for the randomized trial were identified when a physician, hospital, or local public health department in California contacted the California Department of Health Services (CDHS). The project director or principal investigator would then transport the masked, letter-coded study vial containing either BIG-IV or placebo to the hospital, review the medical record, examine the patient, obtain written informed consent for enrollment from the parents, and administer the contents of the vial. The study protocol was approved by the 62 institutional review boards that represented 90 hospitals in California, the Centers for Disease Control and Prevention (CDC), and the State of California Health and Human Services Agency.

The open-label study protocol was approved by the institutional review boards of the California Health and Human Services Agency and 155 participating hospitals, and written informed consent was obtained from the parents of the patients. Patients in the open-label study were eligible to receive BIG-IV any time up to three weeks after hospital admission.

#### STUDY GROUPS

The therapeutic intervention was a single intravenous infusion of either BIG-IV (50 mg per kilogram of body weight [1 ml per kilogram]) or an identical-appearing, conventional, licensed intravenous immune globulin (Gammagard or Gammagard S/D, Baxter International) that did not neutralize botulinum toxin in the mouse bioassay.<sup>1</sup> BIG-IV is a lyophilized powder reconstituted to contain approximately 5 percent human immune globulin with at least 15 IU of neutralizing antibodies against toxin type A and at least 4 IU of neutralizing antibodies against toxin type B per 50 mg. BIG-IV was produced for the CDHS for this study in December 1991 by the Massachusetts Public Health Biologic Laboratories from source plasma collected by the CDHS. Plasma donors were CDHS laboratory workers and colleagues immunized for occupational safety with pentavalent botulinum toxoid (Food and Drug Administration [FDA] In-

vestigational New Drug application 0161) and given a single booster immunization before plasmapheresis.

#### RANDOMIZATION

Each patient was randomly assigned by the study statistician to one of the two study groups with the use of a printed random-number table and a master sequential list that was unavailable to the study investigators. The use of a block size of two accomplished an approximately equal allocation of patients with illness caused by type A toxin and those with illness caused by type B toxin to the two groups of the study as a natural consequence of the random occurrence of type A or type B illness during the five years of the clinical trial. Each patient's sequential study-enrollment number was linked to one of eight letter codes stamped on the study vials; this identified the vial to be used in treatment. Serologic studies to determine the half-life of BIG-IV that were performed after the trial was unblinded confirmed that all vials were administered as assigned.

#### OUTCOME MEASURES

The primary safety outcome for all study subjects, regardless of their eventual status with regard to botulism, was the occurrence of adverse events, including possible allergic reactions and blood-borne infections. The primary efficacy outcome was the duration of hospitalization required, as determined by the following standardized criteria for discharge: no further need for inpatient care for infant botulism or its complications, no need for mechanical ventilation or supplemental oxygen for at least three days, no worsening of paralysis in the previous three days and a demonstrated improvement in motor and bulbar function, and three days of intake by tube feeding of 25 percent or less of maintenance volume and calories, with the remainder consumed by mouth.

Secondary efficacy outcomes included the durations of intensive care, mechanical ventilation, and tube feeding, the number of adverse events, and the total charges for the hospital stay. Before the study was unblinded, adverse events and relevant dates were verified by means of hospital and clinic notes and confirmed by parents, who were informed after unblinding of the treatment allocation of their child.

We designed the study to enroll 120 patients with laboratory-confirmed infant botulism, the

projected number of cases in a three-year period (the maximum length of an initial FDA funding award for the study of orphan drugs). However, the trial took five years to complete because of lower-than-expected incidence and a temporary suspension that followed the recall of unrelated lots of the placebo.<sup>15</sup> This sample size provided 80 percent power at a 5 percent significance level to detect a 42 percent decrease in the mean length of the hospital stay.

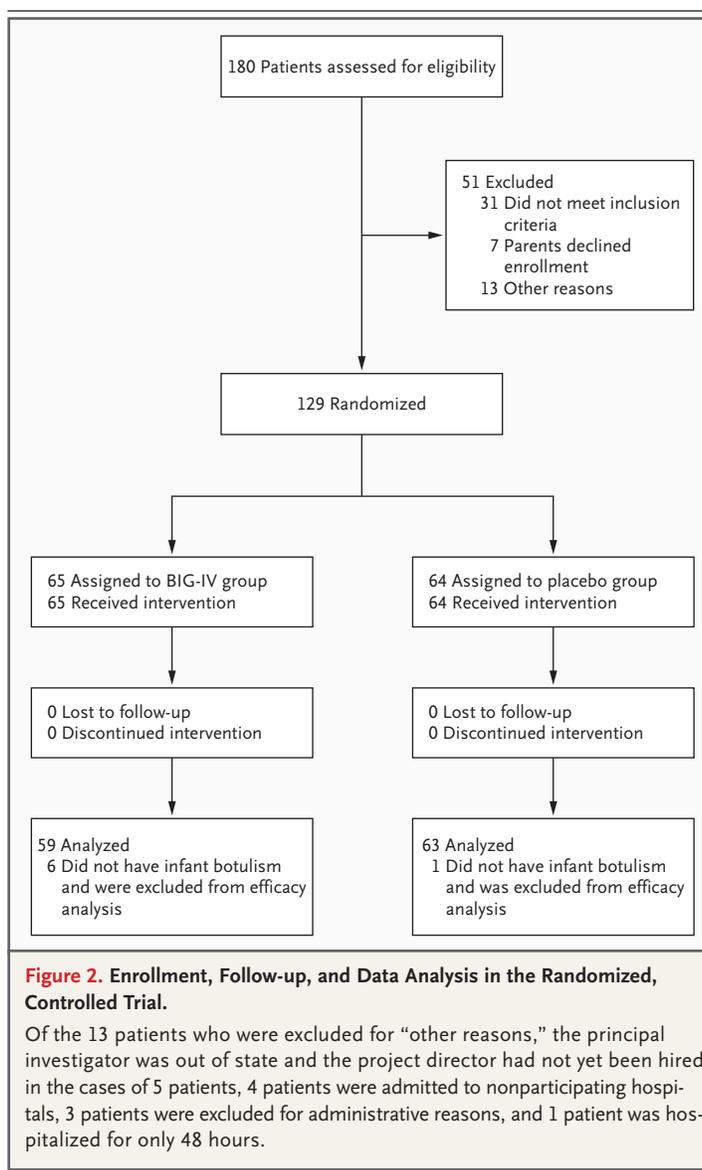
Hospital charges were used as a surrogate for the cost of the illness. They do not include the fees of the attending physicians, unless these were billed through the hospital; the costs of transferring the patient by ambulance and, in the open-label study, occasionally by aircraft between states; or indirect costs to parents such as lost work time and hotel bills. Hospital charges were adjusted annually into current-year dollars according to the lowest percentage increase in medical costs in the previous year (obtained from the Web site of the U.S. Bureau of Labor Statistics, <http://data.bls.gov/cgi-bin/srgate>) in the San Francisco metropolitan area, the Los Angeles metropolitan area, or all cities in the United States, and also, in the open-label study, in the New York–New Jersey metropolitan area or the Philadelphia–New Jersey metropolitan area.

#### LABORATORY TESTING

Fecal and enema samples were tested by established methods for identifying and typing *C. botulinum* toxin and organisms.<sup>1</sup> To determine the half-life of BIG-IV, serum samples obtained from patients in the randomized trial before infusion and after infusion at regular intervals for a period of 28 weeks were measured for levels of IgG against botulinum toxin type A and type B. We developed at the CDC a double-sandwich enzyme-linked immunosorbent assay that used purified botulinum toxin type A or type B as the capture antigen, in order to measure the sequential anti-A toxin antibody concentrations in the patients with type B illness and the sequential anti-B toxin antibody concentrations in the patients with type A illness. The results of serologic testing were withheld from the CDHS investigators until the study was unblinded.

#### STATISTICAL ANALYSIS

Outcome measures for the randomized trial were analyzed by the nonparametric Kolmogorov–



Smirnov test<sup>16</sup> (requested by the FDA after the conclusion of enrollment) and by the t-test (pre-planned), as permitted on the basis of the relatively large sample sizes ( $\geq 20$  patients). Statistical analyses with the use of Stata software, version 8.0 (StataCorp), were based on the intention-to-treat population as initially assigned. Seven patients without laboratory-confirmed infant botulism were excluded prospectively from the efficacy analysis but were included in the safety analysis. A single, prespecified interim analysis was performed after 60 patients had been enrolled and was adjusted for in the final analysis. Linear regression techniques were used to adjust for the

random differences between the placebo and BIG-IV groups.

## RESULTS

### RANDOMIZED CLINICAL TRIAL

A total of 180 patients were evaluated for eligibility, and 129 were enrolled in the clinical trial (Fig. 2). Of these, 122 participants had laboratory-confirmed infant botulism and could be evaluated for all outcome measures. Sixty-three patients received the placebo immune globulin, and

59 patients received BIG-IV. The baseline characteristics of the two groups were similar, except that infants in the BIG-IV group were older and weighed more than infants in the control group. The proportions of patients with type A illness and patients with type B illness in the two groups were similar (Table 1). Before the study was unblinded, determination of the length of the hospital stay on the basis of prespecified discharge criteria resulted in the exclusion of 18 of 3603 hospital days (0.5 percent; 12 in the placebo group and 6 in the BIG-IV group).

Treatment with BIG-IV decreased the mean length of the hospital stay, the primary efficacy outcome variable, from 5.7 weeks to 2.6 weeks ( $P<0.001$ ) (Table 2). The median length of the hospital stay decreased from 4.0 weeks to 1.9 weeks ( $P<0.001$ ). The mean total hospital charges per patient decreased from \$163,400 to \$74,800 (in 2004 U.S. dollars;  $P<0.001$ ). The secondary outcome measures — duration of intensive care, duration of mechanical ventilation, and duration of tube or intravenous feeding — were also significantly shorter in the BIG-IV group (Table 2).

In preplanned subgroup analyses, BIG-IV conferred benefits regardless of whether the patients had type A illness or type B illness. Untreated type A illness was more severe than untreated type B illness, as measured by the mean durations of the hospital stay, intensive care, mechanical ventilation, and tube or intravenous feeding (Table 2). BIG-IV treatment shortened the mean length of the hospital stay by 3.8 weeks ( $P=0.004$ ) for patients with type A illness, and by 2.0 weeks ( $P<0.001$ ) for patients with type B illness. BIG-IV also shortened the mean duration of intensive care, mechanical ventilation, and tube or intravenous feeding, as well as the mean hospital charges per patient in both subgroups (Table 2).

The safety analysis included 129 infants. No patient had bronchospasm or an anaphylactic reaction from the study infusion. The only adverse event perhaps related to BIG-IV was a transient, blush-like rash that also occurred in patients with untreated infant botulism (Table 3). The frequency of new urinary tract infections and anemia requiring therapy was lower in the BIG-IV group than in the control group ( $P<0.05$ ) (Table 3). One death occurred five months after treatment with placebo in a patient whose weakness was eventually diagnosed as resulting from spinal muscular atrophy (Werdnig–Hoffmann disease).

**Table 1. Baseline Characteristics of Infants in the Randomized Trial.**

Characteristic	Placebo Group (N=63)	BIG-IV Group (N=59)	P Value*
Age at onset of symptoms (days)			
Mean	105	131	0.02
Range	26–188	21–313	—
Mean weight (kg)	5.9	6.7	0.01
Male sex (%)	32	47	0.08
Race or ethnic group (%)†			
White	63	59	0.64
Hispanic	22	27	—
Asian or Pacific Islander	10	12	—
Black	2	0	—
Other	3	2	—
Exposed to honey (%)‡	5	7	0.63
Breast-fed at onset of symptoms (%)§	84	92	0.27
Botulinum toxin (%)			
Type A	60	62	0.79
Type B	40	38	
Mean time from onset of symptoms (days)			
To admission	2.8	2.9	0.84
To study infusion	4.3	4.2	0.97
Intubated between admission and day of infusion (%)	37	34	0.85
Admitted only to community hospital (%)	6	10	0.99
Suspected at admission of having infant botulism (%)	49	53	0.35

\* P values are calculated with a t-test or Fisher's exact test; both were two-sided. Dashes denote not applicable.

† The P value is for the comparison of white with all other categories. Race or ethnic group was self-assigned by each mother.

‡ Honey ingestion is a recognized risk factor for infant botulism.<sup>17</sup>

§ Breast-feeding provides protection against fulminant-onset illness.<sup>18</sup>

**Table 2. Primary and Secondary Efficacy Results of the Randomized, Controlled Trial of BIG-IV.\***

Outcome Variable	All Patients			Patients with Type A Illness			Patients with Type B Illness		
	No. of Patients	Mean (95% CI)	P Value†	No. of Patients	Mean (95% CI)	P Value†	No. of Patients	Mean (95% CI)	P Value†
Length of hospital stay (wk)									
Placebo group	63	5.7 (4.4 to 7.0)		38	6.7 (4.7 to 8.7)		25	4.2 (3.3 to 5.0)	
BIG-IV group	59	2.6 (2.0 to 3.3)		37	2.9 (2.2 to 3.6)		22	2.2 (0.9 to 3.6)	
Difference in means		3.1 (1.6 to 4.5)	<0.001, <0.001		3.8 (1.7 to 5.9)	0.004, <0.001		2.0 (0.4 to 3.4)	<0.001, 0.02
Adjusted difference in means‡		3.3	<0.001, <0.001		4.0	0.004, <0.001		2.0	<0.001, 0.02
Length of ICU stay (wk)§									
Placebo group	45	5.0 (3.4 to 6.6)		25	6.5 (3.8 to 9.2)		20	3.1 (2.4 to 3.8)	
BIG-IV group	45	1.8 (1.2 to 2.3)		26	1.9 (1.2 to 2.5)		19	1.6 (0.5 to 2.6)	
Difference in means		3.2 (1.6 to 4.9)	<0.001, <0.001		4.6 (2.0 to 7.3)	0.004, 0.002		1.5 (0.3 to 2.8)	<0.001, 0.02
Duration of mechanical ventilation (wk)¶									
Placebo group	35	4.4 (3.0 to 5.8)		18	6.4 (4.1 to 8.8)		17	2.2 (1.6 to 2.2)	
BIG-IV group	24	1.8 (1.2 to 2.4)		13	2.0 (1.3 to 2.8)		11	1.5 (0.4 to 2.5)	
Difference in means		2.6 (0.9 to 4.3)	0.01, 0.001		4.4 (1.6 to 7.2)	0.001, 0.001		0.7 (-0.4 to 1.8)	0.03, 0.20
Duration of tube or intravenous feeding (wk)									
Placebo group	63	10.0 (6.8 to 13.1)		38	13.4 (8.6 to 18.3)		25	4.7 (3.3 to 6.0)	
BIG-IV group	59	3.6 (1.7 to 5.5)		37	3.5 (2.4 to 4.6)		22	3.8 (-1.3 to 9.0)	
Difference in means		6.4 (2.7 to 10.0)	<0.001, <0.001		9.9 (5.0 to 15.0)	<0.001, <0.001		0.9 (-4.4 to 6.1)	<0.001, 0.75
No. of adverse events per patient									
Placebo group	63	1.7 (1.1 to 2.2)		38	1.8 (1.0 to 2.6)		25	1.4 (0.5 to 2.3)	
BIG-IV group	59	0.9 (0.4 to 1.4)		37	1.0 (0.3 to 1.6)		22	0.8 (0.2 to 1.4)	
Difference in means		0.8 (0.1 to 1.5)	0.07, 0.04		0.8 (-0.2 to 1.9)	0.21, 0.10		0.6 (-0.4 to 1.6)	0.48, 0.25
Total hospital charges per patient (\$)									
Placebo group	63	163,400 (123,000 to 203,700)		38	182,900 (121,700 to 244,100)		25	133,700 (89,700 to 177,700)	
BIG-IV group	59	74,800 (50,600 to 99,100)		37	74,900 (47,400 to 102,500)		22	74,700 (25,500 to 123,900)	
Difference in means		88,600 (41,200 to 136,000)	<0.001, <0.001		108,000 (41,400 to 174,600)	0.006, 0.002		59,000 (-4,900 to 123,000)	0.001, 0.07

\* CI denotes confidence interval, and ICU intensive care unit.  
 † The first P value was determined with use of the Kolmogorov-Smirnov test, and the second with use of the t-test.  
 ‡ The difference in means was adjusted for age at onset and weight at admission.  
 § The length of ICU stay was for patients who had been in the ICU at any time.  
 ¶ The duration of mechanical ventilation was for patients who had been on mechanical ventilation at any time.  
 || Charges have been adjusted to 2004 U.S. dollars and rounded.

**Table 3. Adverse Events and Serious Adverse Events among Infants in the Randomized, Controlled Trial.\***

Event	BIG-IV Group (N = 65)	Placebo Group (N = 64)
no. (%)		
<b>Adverse event</b>		
Patients with $\geq 1$ adverse event		
At enrollment	19 (29)	12 (19)
$\leq 24$ hr after product infusion	5 (8)	4 (6)
$>24$ hr after product infusion	17 (26)	28 (44) <sup>†</sup>
Transient erythematous rash		
During and $<24$ hr after infusion	9 (14)	2 (3)
$\geq 1$ Day after infusion	11 (17)	12 (19)
Otitis media	6 (9)	6 (9)
<b>Serious adverse event</b>		
Pneumonia	6 (9)	10 (16)
Respiratory arrest	1 (2)	6 (9)
Anemia	2 (3)	10 (16) <sup>†</sup>
Hyponatremia	3 (5)	9 (14)
Urinary tract infection	1 (2)	8 (12) <sup>†</sup>
Tracheal stenosis	3 (5)	1 (2)
Seizures	0	3 (5)
Long-bone fracture <sup>‡</sup>	0	3 (5)
Hypertension	0	3 (5)
Hypotension	0	2 (3)
Hypothermia	2 (3)	0
<i>Clostridium difficile</i> colitis	1 (2)	1 (2)
Toxic megacolon and shock	1 (2)	0
Pneumothorax	0	2 (3)
Febrile reaction to transfusion	0	1 (2)
Pneumomediastinum	0	1 (2)
Subcutaneous emphysema	0	1 (2)
Acute respiratory distress syndrome	0	1 (2)
Bacteremia	0	1 (2)
Aspiration pneumonitis	0	1 (2)
Respiratory syncytial virus bronchiolitis	0	1 (2)

\* Adverse events are those that occurred during and after infusion.

<sup>†</sup>  $P < 0.05$  by a two-sided Fisher's exact test.

<sup>‡</sup> Long-bone fractures were presumed to be caused by osteomalacia resulting from prolonged paralysis.

The mean elimination half-lives of the anti-A toxin and anti-B toxin antibodies were 27.3 days (measured in 26 patients) and 27.9 days (15 patients), respectively. The mean ( $\pm$ SD) half-life of BIG-IV accordingly was determined to be  $27.7 \pm 9.3$  days (41 patients).

#### OPEN-LABEL STUDY

BIG-IV was given on an open-label basis to 382 patients with laboratory-confirmed infant botulism in 128 hospitals located in 37 states. For the 366 patients treated within 7 days of hospital admission, the mean length of hospital stay was 2.2 weeks (2.5 weeks for 146 patients with type A illness, and 2.1 weeks for 220 patients with type B illness) (Table 4). BIG-IV treatment given within 3 days of hospital admission (to 287 patients) shortened the mean length of the hospital stay to 2.0 weeks, which was significantly shorter than the mean stay of 2.9 weeks when treatment was given 4 to 7 days after hospital admission (to 79 patients;  $P < 0.001$ ) (Table 4). Mean hospital charges per patient for the 366 patients were \$57,900, and a total of 20.3 years of hospital stay and \$34.2 million in hospital charges were avoided through open-label use of BIG-IV (Table 4).

Patients in the open-label study had adverse events that were similar in nature and frequency to those in the randomized trial, and they were not considered causally related to treatment with BIG-IV. Seven patients in the open-label study died. Five of these patients were found not to have infant botulism and died from their actual causes of weakness (e.g., spinal muscular atrophy and mitochondrial disorder) weeks or months after treatment with BIG-IV. Of the two patients with confirmed infant botulism, one died from a concomitant neuroblastoma, and the other from hypoxic cerebral injury after a cardiopulmonary arrest that occurred before BIG-IV was given.

#### DISCUSSION

Treatment of patients with infant botulism type A or type B with BIG-IV in a five-year, randomized, controlled clinical trial reduced the mean length of the hospital stay for all patients by 3.1 weeks. The mean length of stay in the intensive care unit, the mean duration of mechanical ventilation, the mean duration of tube or intravenous feeding, and the mean hospital charges per patient were also significantly reduced in infants treated with BIG-IV. The only adverse effect perhaps related to treatment with BIG-IV was a transient, blush-like erythematous rash. No serious adverse events occurred more commonly in infants treated with BIG-IV than in those treated with placebo.

The reduction in the mean length of the hospital stay in patients treated with BIG-IV and the

safety attributes of BIG-IV in the randomized trial were confirmed in the subsequent six-year nationwide, open-label study. In that study, treatment with BIG-IV given within 3 days after hospital admission shortened the mean length of the hospital stay by approximately 1 week more than did treatment with BIG-IV given 4 to 7 days after admission (2.0 vs. 2.9 weeks). The total length of hospital stays and total hospital charges avoided during the nationwide open-label study were 20.3 years and \$34.2 million (in 2004 U.S. dollars), respectively.

Keen clinical awareness may be needed to recognize this rare disease, since infant botulism was suspected at admission in only half the infants enrolled in the randomized trial. Also, infant botulism may present as, or quickly may become, a life-threatening illness. Almost three quarters of the infants in the randomized trial needed intensive care, approximately half of them needed mechanical ventilation, and many had serious complications. However, treatment with BIG-IV did not always result in a shortened hospital stay. One patient with type A illness who received BIG-IV treatment acquired a nosocomial *C. difficile* infection that was complicated by pseudomembranous colitis, toxic megacolon, and shock; this patient was hospitalized for 12.4 weeks.<sup>19</sup> Acquired *C. difficile* complicating infant botulism may occur more frequently than is generally appreciated.<sup>20</sup> One patient with type B illness who received BIG-IV treatment required surgical repair of tracheal stenosis that followed endotracheal intubation; her several hospital stays totaled 15.4 weeks.

BIG-IV has a half-life of approximately 28 days in vivo and a large capacity to neutralize botulinum toxin. A single infusion will neutralize for at least six months all botulinum toxin that may be absorbed from the colon of an infant. This feature is particularly important because it renders moot the concern that antibiotics used to treat secondary bacterial infections may lyse *C. botulinum* vegetative cells in the intestinal lumen and thereby increase the amount of botulinum toxin available for absorption.<sup>21</sup>

Although commercial equine botulinum antitoxin has been available in the United States since 1940,<sup>22</sup> its efficacy has never been evaluated in a controlled trial. In retrospective and observational studies, early administration of equine antitoxin to adult patients with foodborne and wound botulism

**Table 4. Hospital Stay and Hospital Charges Avoided by Open-Label Treatment with BIG-IV within Seven Days after Hospital Admission, 1997 to 2003.\***

Variable	No. of Patients	Mean Length of Hospital Stay (wk)	Mean Length of Hospital Stay Avoided (wk)	Total Length of Hospital Stay Avoided (yr)	No. of Patients	Mean Hospital Charges (\$) <sup>†</sup>	Mean Hospital Charges Avoided (\$) <sup>‡</sup>	Total Hospital Charges Avoided (\$) <sup>‡</sup>
All patients	366	2.2 <sup>‡</sup>	3.5	20.3 <sup>§</sup>	357 <sup>¶</sup>	57,900	105,400	34,174,200 <sup>  </sup>
Patients with toxin type A	146	2.5	4.0	11.3	145	58,900	123,900	17,973,900
Patients with toxin type B	220	2.1	2.1	9.0	212	57,300	76,400	16,200,300
Patients treated on hospital days 0 to 3	287	2.0 <sup>‡</sup>	3.7	20.4	278 <sup>¶</sup>	55,400	107,900	29,996,200
Patients treated on hospital days 4 to 7	79	2.9 <sup>‡</sup>	NC <sup>  </sup>	NC <sup>  </sup>	79	67,000	NC <sup>  </sup>	NC <sup>  </sup>

\* The reference group is the placebo group from the randomized, clinical trial conducted in 1992 to 1997.

<sup>†</sup> All charges are in 2004 U.S. dollars and have been rounded.

<sup>‡</sup> P<0.001 for the comparison of the mean length of hospital stay for patients treated on hospital days 0 to 3 and those treated on hospital days 4 to 7. Also, P<0.001 for the comparison of the mean length of hospital stay for patients treated on hospital days 0 to 7 and the mean length of hospital stay of 5.7 weeks for placebo-treated patients in the randomized, clinical trial.

<sup>§</sup> The "All patients" totals are weighted averages obtained by adding the totals for patients with type A illness to those for patients with type B illness.

<sup>¶</sup> Nine patients (one with type A illness and eight with type B illness) were excluded because of incomplete information about hospital charges.

<sup>||</sup> NC denotes not calculated. All patients in the randomized, clinical trial were treated within 0 to 3 days of hospital admission.

was associated with improved outcomes.<sup>23,24</sup> However, approximately 6 percent of adults with foodborne botulism had anaphylaxis or serum sickness when treated with one or two vials of equine botulism antitoxin<sup>13</sup>; such treatment would not be suitable for infants. Because botulinum toxin is now categorized as a category A (maximum threat) bioweapon,<sup>25</sup> a larger supply of fully human-compatible botulism antitoxin than can be obtained by plasmapheresis is needed,<sup>26</sup> and a suitable recombinant product is under development.<sup>27</sup>

We conclude that BIG-IV, now licensed by the FDA to CDHS as BabyBIG, is a safe and effective treatment for infant botulism type A and type B. Treatment should be given as soon as possible after hospital admission and should not be delayed for confirmatory testing of feces or enema. BabyBIG is available as a public-service orphan drug in the United States. (Information on this drug may be obtained at [www.infantbotulism.org](http://www.infantbotulism.org) and by telephone from the CDHS Infant Botulism Treatment and Prevention Program at 510-231-7600.)

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#### REFERENCES

1. Botulism in the United States, 1899-1996: handbook for epidemiologists, clinicians, and laboratory workers. Atlanta: Centers for Disease Control and Prevention, 1998. (Accessed January 6, 2006, at <http://www.bt.cdc.gov/agent/botulism/index.asp>.)
2. Wilcke BW Jr, Midura TF, Arnon SS. Quantitative evidence of intestinal colonization by *Clostridium botulinum* in four cases of infant botulism. *J Infect Dis* 1980; 141:419-23.
3. Arnon SS, Midura TF, Clay SA, Wood RM, Chin J. Infant botulism: epidemiological, clinical, and laboratory aspects. *JAMA* 1977;237:1946-51.
4. Schiavo G, Matteoli M, Montecucco C. Neurotoxins affecting neuroexocytosis. *Physiol Rev* 2000;80:717-66.
5. Simpson LL. Identification of the major steps in botulinum toxin action. *Annu Rev Pharmacol Toxicol* 2004;44:167-93.
6. Long SS, Gajewski JL, Brown LW, Gilligan PH. Clinical, laboratory, and environmental features of infant botulism in southeastern Pennsylvania. *Pediatrics* 1985; 75:935-41.
7. Schreiner MS, Field E, Ruddy R. Infant botulism: a review of 12 years' experience at the Children's Hospital of Philadelphia. *Pediatrics* 1991;87:159-65.
8. Nevas M, Lindstrom M, Virtanen A, et al. Infant botulism acquired from household dust presenting as sudden infant death syndrome. *J Clin Microbiol* 2005;43: 511-3.
9. Arnon SS. Infant botulism. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds. *Textbook of pediatric infectious diseases*. 5th ed. Philadelphia: W.B. Saunders, 2004:1758-66.
10. Gill DM. Bacterial toxins: a table of lethal amounts. *Microbiol Rev* 1982;46:86-94.
11. Barash JR, Tang TWH, Arnon SS. First case of infant botulism caused by *Clostridium baratii* type F in California. *J Clin Microbiol* 2005;43:4280-2.
12. Barash JR, Arnon SS. Dual toxin-producing strain of *Clostridium botulinum* type Bf isolated from a California patient with infant botulism. *J Clin Microbiol* 2004; 42:1713-5.
13. Black RE, Gunn RA. Hypersensitivity reactions associated with botulinum antitoxin. *Am J Med* 1980;69:567-70.
14. Hatheway CH, Snyder JD, Seals JE, Edell TA, Lewis GE Jr. Antitoxin levels in botulism patients treated with trivalent equine botulism antitoxin to toxin types A, B, and E. *J Infect Dis* 1984;150:407-12.
15. Outbreak of hepatitis C associated with intravenous immunoglobulin administration — United States, October 1993–June 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:505-9.
16. Conover WJ. *Practical nonparametric statistics*. 2nd ed. New York: John Wiley, 1980.
17. Arnon SS, Midura TF, Damus K, Thompson B, Wood RM, Chin J. Honey and other environmental risk factors for infant botulism. *J Pediatr* 1979;94:331-6.
18. Arnon SS, Damus K, Thompson B, Midura TF, Chin J. Protective role of human milk against sudden death from infant botulism. *J Pediatr* 1982;100:568-73.
19. Schechter R, Peterson B, McGee J, Idowu O, Bradley J. *Clostridium difficile* colitis associated with infant botulism: near-fatal case analogous to Hirschsprung's enterocolitis. *Clin Infect Dis* 1999;29:367-74.
20. Fencia L, Da Dalt L, Anniballi F, Franciosa G, Zanonato S, Aureli P. A case of infant botulism due to neurotoxicogenic *Clostridium butyricum* type E associated with *Clostridium difficile* colitis. *Eur J Clin Microbiol Infect Dis* 2002;21:736-8.
21. Johnson RO, Clay SA, Arnon SS. Diagnosis and management of infant botulism. *Am J Dis Child* 1979;133:586-93.
22. Cooper MS. Antitoxins to *C. botulinum*. In: Lewis KH, Cassel K Jr, eds. *Botulism:*

- proceedings of a symposium. Cincinnati: Public Health Service, 1964:147-64. (USPHS publication no. 999-FP-1.)
23. Tacket CO, Shandera WX, Mann JM, Hargrett NT, Blake PA. Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med* 1984;76:794-8.
24. Chang GY, Ganguly G. Early antitoxin treatment in wound botulism results in better outcome. *Eur Neurol* 2003;49:151-3.
25. 42 Code of Federal Regulations, Part 73. Possession, use and transfer of select agents and toxins (final rule). *Fed Regist* 2005;70:13294-325.
26. Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 2001;285:1059-70.
27. Nowakowski A, Wang C, Powers DB, et al. Potent neutralization of botulinum neurotoxin by recombinant oligoclonal antibody. *Proc Natl Acad Sci U S A* 2002;99:11346-50.

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