

ORIGINAL ARTICLE

Aggressive vs. Conservative Phototherapy for Infants with Extremely Low Birth Weight

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ABSTRACT

BACKGROUND

It is unclear whether aggressive phototherapy to prevent neurotoxic effects of bilirubin benefits or harms infants with extremely low birth weight (1000 g or less).

METHODS

We randomly assigned 1974 infants with extremely low birth weight at 12 to 36 hours of age to undergo either aggressive or conservative phototherapy. The primary outcome was a composite of death or neurodevelopmental impairment determined for 91% of the infants by investigators who were unaware of the treatment assignments.

RESULTS

Aggressive phototherapy, as compared with conservative phototherapy, significantly reduced the mean peak serum bilirubin level (7.0 vs. 9.8 mg per deciliter [120 vs. 168 μmol per liter], $P < 0.01$) but not the rate of the primary outcome (52% vs. 55%; relative risk, 0.94; 95% confidence interval [CI], 0.87 to 1.02; $P = 0.15$). Aggressive phototherapy did reduce rates of neurodevelopmental impairment (26%, vs. 30% for conservative phototherapy; relative risk, 0.86; 95% CI, 0.74 to 0.99). Rates of death in the aggressive-phototherapy and conservative-phototherapy groups were 24% and 23%, respectively (relative risk, 1.05; 95% CI, 0.90 to 1.22). In preplanned subgroup analyses, the rates of death were 13% with aggressive phototherapy and 14% with conservative phototherapy for infants with a birth weight of 751 to 1000 g and 39% and 34%, respectively (relative risk, 1.13; 95% CI, 0.96 to 1.34), for infants with a birth weight of 501 to 750 g.

CONCLUSIONS

Aggressive phototherapy did not significantly reduce the rate of death or neurodevelopmental impairment. The rate of neurodevelopmental impairment alone was significantly reduced with aggressive phototherapy. This reduction may be offset by an increase in mortality among infants weighing 501 to 750 g at birth. (ClinicalTrials.gov number, NCT00114543.)

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IT IS CONTROVERSIAL WHETHER MODEST elevations of total serum bilirubin (hereafter referred to simply as “bilirubin”) cause brain damage in preterm infants.¹⁻⁴ Some observational studies of preterm infants have suggested that bilirubin levels as low as 5 mg per deciliter (86 μmol per liter) or even lower may cause neurodevelopmental deficits.⁵⁻⁸ However, other observational studies have suggested that moderately higher bilirubin levels have no neurotoxic effects⁹⁻¹¹ or might even benefit these infants,¹² because bilirubin is an antioxidant.

Phototherapy is considered to be effective and safe in reducing bilirubin levels.¹³ However, it has been studied in only one large, randomized trial involving infants treated in the 1970s.¹⁴ No neurodevelopmental benefits were identified,¹⁵ and the findings suggested the possibility that phototherapy might increase the risk of death relative to that among controls in the same birth-weight stratum: for birth weight below 2500 g, the relative risk was 1.32 (95% confidence interval [CI], 0.96 to 1.82); for birth weight below 1000 g, the relative risk was 1.49 (95% CI, 0.93 to 2.40).^{16,17} Since that trial was reported, the levels of irradiance delivered by phototherapy lamps have substantially increased, with uncertain effects on the risks and benefits of phototherapy.

We conducted a multicenter, randomized trial comparing the effect of aggressive phototherapy as compared with conservative phototherapy on the incidence of death or neurodevelopmental impairment among infants of extremely low birth weight at 18 to 22 months after the expected date of delivery (the corrected age).

METHODS

The institutional review boards at RTI International and all 16 Neonatal Research Network clinical centers (see the Appendix) approved the study. Written informed consent was obtained from the parent or guardian of each participant.

PATIENTS

Infants with a birth weight of 501 to 1000 g were eligible for enrollment between 12 and 36 hours of age. Exclusion criteria were a terminal condition (defined as a pH <6.8 or persistent bradycardia with hypoxemia for >2 hours), previous phototherapy, a major congenital anomaly, hydrops fetalis or severe hemolytic disease, congenital

nonbacterial infection, or a judgment that the parents would be unable or unlikely to return for assessments at 18 to 22 months.

ENROLLMENT AND TREATMENT

Infants were stratified on the basis of birth weight (501 to 750 g or 751 to 1000 g) and center and were then randomly assigned to a treatment group by means of a centralized computer system. The protocol stipulated the use of phototherapy during the first 14 days after birth. In both groups, phototherapy was provided for at least 24 consecutive hours after it was started or restarted.

For infants in the aggressive-phototherapy group, phototherapy was initiated at enrollment (when the bilirubin level was expected to be approximately 5 mg per deciliter). For infants with a birth weight of 501 to 750 g, the aggressive phototherapy was continued or restarted whenever the bilirubin level was found to be 5 mg per deciliter or higher. For infants with a birth weight of 751 to 1000 g, the aggressive phototherapy was continued or restarted whenever the bilirubin level was found to be 5 mg per deciliter or higher during the first 7 days after birth and 7 mg per deciliter (120 μmol per liter) or higher during the next 7 days. Conservative phototherapy was initiated, continued, or restarted whenever the bilirubin level was 8 mg per deciliter (137 μmol per liter) or higher for infants weighing 501 to 750 g at birth and 10 mg per deciliter (171 μmol per liter) or higher for infants weighing 751 to 1000 g at birth.

A baseline bilirubin level was measured within 4 hours before or at enrollment for the first 100 infants enrolled in each treatment group. Bilirubin was measured at least once daily for the first 7 days after birth for all infants. During the second week after birth, bilirubin was measured on any day on which phototherapy was administered or when phototherapy had been stopped in the previous 24 hours or the last bilirubin measurement exceeded 5 mg per deciliter for infants with a birth weight of 501 to 750 g or 7 mg per deciliter for infants with a birth weight 751 to 1000 g. A parent or guardian of 1101 infants consented to the collection of an additional blood sample on day 5 of the treatment period, which was sent to Stanford University or Brown University for assay of the serum level of unbound bilirubin according to the Arrow technique.¹⁸ Un-

bound bilirubin (which accumulates when the bilirubin-binding capacity of albumin has been exceeded) was assessed because the neurotoxic effects of bilirubin are thought to be caused by entry of unbound bilirubin into the brain.¹⁸

On the basis of current phototherapy recommendations and practice,¹³ the target irradiance level was 15 to 40 μW per square centimeter per nanometer of wavelength and was measured by research personnel and bedside nurses. Irradiance levels were increased, within this range, if the bilirubin level exceeded 13 mg per deciliter (222 μmol per liter) for infants with a birth weight of 501 to 750 g and 15 mg per deciliter (256 μmol per liter) for infants with a birth weight of 751 to 1000 g. An exchange transfusion was indicated for any infant whose bilirubin level exceeded the threshold after 8 hours of this intensified treatment. The study was designed as an effectiveness trial,¹⁹ and the brand and number of phototherapy lights, administration of fluids, feedings, and other interventions were chosen at the discretion of the caregivers.

ASSESSMENTS

Research nurses recorded all data using standardized definitions. Bronchopulmonary dysplasia was identified by the administration of supplemental oxygen therapy at 36 weeks of postmenstrual age. Outcomes at 18 to 22 months of corrected age were assessed by neurologic examiners and neurodevelopmental testers who had been trained for reliability of assessments during a 2-day workshop and were unaware of the treatment assignments.²⁰

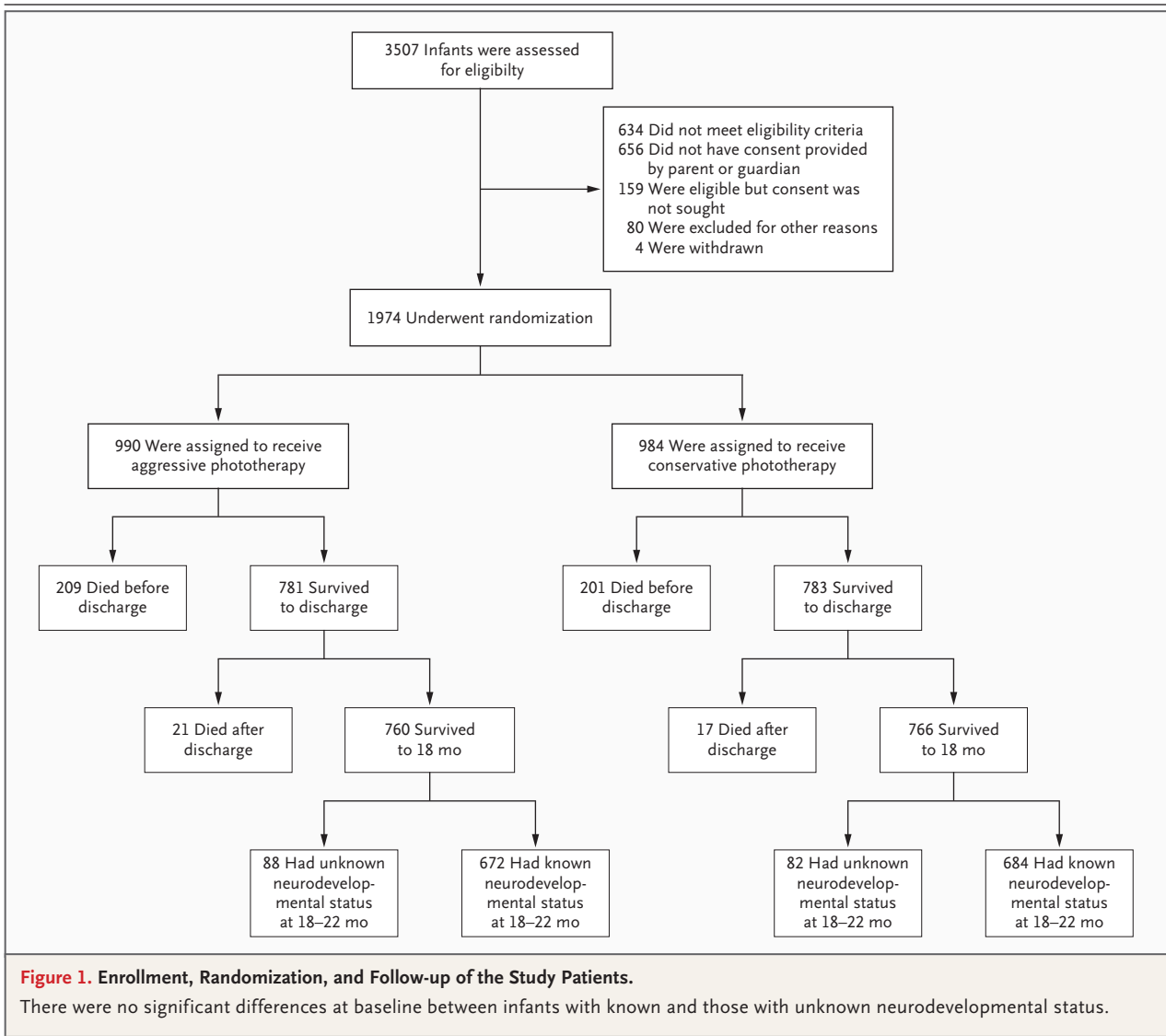
The primary outcome was death or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as blindness (no functional vision in either eye), severe hearing loss (hearing loss for which bilateral hearing aids were prescribed), moderate or severe cerebral palsy, or a score below 70 on the Mental or Psychomotor Developmental Index of the Bayley Scales of Infant Development II (on which scores can range from 50 to 150, with 150 indicating the most advanced development).²¹ Secondary outcomes included each of the individual outcomes above and predefined clinical

diagnoses or potential adverse events. Cerebral palsy was defined as a nonprogressive disorder of the central nervous system characterized by abnormal muscle tone in at least one arm or leg and abnormal control of movement or posture with delayed attainment of motor milestones. Infants were classified as having moderate or severe cerebral palsy if they were able to walk only with assistive devices or were unable to walk at all, respectively. Hearing outcomes were determined by the neurologic examiner and reports by parents or guardians. If a hearing loss was present, more information was collected to determine the nature of the deficit and whether hearing aids were prescribed. In post hoc analyses, we used a definition of profound impairment that was similar to the definition in a previous analysis by our group²²: a score on the Mental or Psychomotor Developmental Index of 50 or less or a level of 5 for gross motor function, according to the modified criteria of Palisano et al.²³ (on which the level of motor function can range from 0 to 5, with 5 indicating that movement requires assistance by an adult).

STATISTICAL ANALYSIS

A difference of 7 percentage points between the two treatment groups in the rate of the primary outcome was considered clinically important. To detect this difference with an alpha value of 0.05 and a statistical power of 0.80, we planned to study 1976 infants. Intention-to-treat analyses were performed. The denominator used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Analyses were conducted at the Neonatal Research Network data coordinating center, at RTI International, and were adjusted for the stratification variables (birth weight and center) with the use of robust Poisson regression analyses to estimate the adjusted relative risk. Additional regression analyses involved adjustment for the infants' sex, race or ethnic group, and location of birth (within or outside of the network center). To assess whether differences between groups might be explained by differences in rates of bronchopulmonary dysplasia between the two groups, separate regression analyses were performed in which bronchopulmonary dysplasia was added as a predictor variable.

Prespecified subgroup analyses were conducted for each birth-weight stratum. We included an



interaction term for birth-weight stratum with treatment group and assessed the statistical significance of the interaction term. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Analyses did not include adjustment for multiple comparisons.²⁴

Our findings prompted us to perform post hoc analyses of profound impairment, as well as Bayesian analyses²⁵⁻²⁹ of overall outcomes and outcomes according to birth-weight stratum³⁰ (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). No other post hoc analyses were performed.

RTI International tracked hearing assessments and deaths before discharge, since data for the

primary outcome would not be available before 18 to 22 months. An independent data and safety monitoring committee reviewed the interim results, including those concerning adverse outcomes, four times. Pocock boundaries were used to develop stopping rules for interim safety monitoring of death and for hearing loss. The nominal significance level was 0.05 and the critical P value for each review was set at 0.0158.

RESULTS

Between September 2002 and April 2005, we enrolled 1974 (69%) of 2873 eligible infants (Fig. 1). The aggressive-phototherapy group and the con-

servative-phototherapy group were generally similar, with small differences in the percentages of male infants and black infants (Table 1).

As expected, the two groups differed significantly in mean and peak bilirubin levels, unbound bilirubin on day 5, and the duration of phototherapy (Table 2). The proportion of infants receiving phototherapy and the mean bilirubin levels are shown according to day after birth and treatment group in Fig. 1A and 1B in the Supplementary Appendix. Phototherapy was never given to 1 of the 990 infants (<1%) in the aggressive-phototherapy group and to 215 of the 984 infants (22%) in the conservative-phototherapy group. Among infants who did receive phototherapy, the mean irradiance levels were 22 to 23 μW per square centimeter per nanometer each day.

The bilirubin level in 3 infants in the aggressive-phototherapy group and 13 in the conservative-phototherapy group exceeded the threshold, resulting in intensified phototherapy. Two infants receiving aggressive phototherapy and 3 receiving conservative phototherapy received an exchange transfusion; an additional infant in each group who met criteria for exchange transfusion did not undergo the procedure, on the basis of the judgment of the attending neonatologist.

The rates of prespecified secondary outcomes before hospital discharge are shown in Table 2. The relative risks for bronchopulmonary dysplasia and the composite outcome of bronchopulmonary dysplasia or death were significantly reduced with aggressive phototherapy as compared with conservative phototherapy, but those for the other 12 predischarge outcomes were not. The relative risks shown in Table 2 changed only minimally in analyses that involved adjustment for race or ethnic group, sex, and location of birth of infants (data not shown).

OUTCOMES AT 18 TO 22 MONTHS

The primary outcome of death or neurodevelopmental impairment was determined for 1804 infants (91% of the 1974 who underwent randomization); whether the infant died was known for 1890 (96%). The proportion of infants with the primary outcome was 52% in the aggressive-phototherapy group and 55% in the conservative-phototherapy group (relative risk, 0.94; 95% CI, 0.87 to 1.02; $P=0.15$) (Table 3). (The relative risk in analyses that were also adjusted for race or ethnic

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aggressive Phototherapy (N=990)	Conservative Phototherapy (N=984)
Birth weight — g	777 \pm 134	777 \pm 134
Gestational age — wk	26 \pm 2	26 \pm 2
Male sex — no. (%)	486 (49)	527 (54)
Race or ethnic group — no. (%) [†]		
Black	439 (44)	383 (39)
Hispanic	174 (18)	190 (19)
White	349 (35)	369 (38)
Other	28 (3)	42 (4)
Antenatal corticosteroids — no./total no. (%)	783/986 (79)	783/978 (80)
Born in network center — no. (%)	906 (92)	881 (90)
Cesarean delivery — no./total no. (%)	656/990 (66)	627/981 (64)
5-Min Apgar score <5 — no./total no. (%)	136/980 (14)	128/974 (13)
Hematocrit at <12 hr of age — %	43.1 \pm 6.7	43.9 \pm 7.0
Positive result on Coombs test — no./total no. (%)		
Mother	28/680 (4)	31/664 (5)
Infant	8/903 (1)	7/895 (1)
Maternal blood group O — no./total no. (%)	437/946 (46)	440/940 (47)
Maternal Rh positive — no./total no. (%)	825/946 (87)	826/940 (88)
Supplemental oxygen at 24 hr — no./total no. (%)	647/987 (66)	642/983 (65)
Continuous positive airway pressure at 24 hr — no./total no. (%)	209/988 (21)	191/983 (19)
Ventilation at 24 hr — no. (%) [‡]	693/988 (70)	698/983 (71)
Baseline bilirubin in first 100 infants enrolled — mg/dl	4.8 \pm 1.5	5.0 \pm 1.7

* Plus-minus values are means \pm SD. The denominator used to calculate the percentage of infants (or mothers) with a specific characteristic was the number for whom the characteristic was known. This number was the total number in each group unless otherwise specified for percentages of patients and except for hematocrit, for which data were available for 967 infants in the aggressive-phototherapy group and 954 in the conservative-phototherapy group, and for baseline bilirubin, for which data were actually obtained for 101 and 102 infants, respectively. Significant differences were found between the two groups for male sex ($P=0.047$), race or ethnic group ($P=0.049$), and hematocrit at less than 12 hours of age ($P=0.006$). To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

[†] Race or ethnic group was reported by parents or guardians of the patients or was determined by the physician on chart review.

[‡] Ventilation was defined as high-frequency, intermittent mechanical ventilation or nasal synchronized intermittent mechanical ventilation.

group, sex, and location of birth was 0.96 [95% CI, 0.89 to 1.04], $P=0.33$.)

Death occurred in 24% of infants in the aggressive-phototherapy group and 23% of those in the conservative-phototherapy group (relative risk, 1.05; 95% CI, 0.90 to 1.22). The rate of neurode-

Table 2. Findings in Study Patients before or at Discharge.*

Variable or Outcome	Aggressive Phototherapy	Conservative Phototherapy	P Value
Variable			
Total serum bilirubin at start of phototherapy — mg/dl	4.8±1.6	10.0±1.5	<0.001
Daily total serum bilirubin, day 1–14 — mg/dl	4.7±1.1	6.2±1.5	<0.001
Peak total serum bilirubin, day 1–14 — mg/dl	7.0±1.8	9.8±2.1	<0.001
Age at peak bilirubin — hr	95±69	75±45	<0.001
Unbound bilirubin at day 5 — mg/dl	0.33±0.25	0.48±0.33	<0.001
Age when phototherapy started — hr	23±9	58±26	<0.001
Duration of phototherapy — hr	88±48	35±31	<0.001
Exchange transfusions — no.†	2	3	0.69
Days to regain birth weight	12.6±6.2	12.5±6.6	0.65
Length of hospital stay among survivors — days	97±43	100±47	0.11
			Relative Risk (95% CI)‡
Predischarge secondary outcome — no./total no. (%)			
Death before day 15	96/990 (10)	95/984 (10)	1.00 (0.78–1.30)
Death before discharge	209/990 (21)	201/984 (20)	1.03 (0.88–1.21)
Intraventricular hemorrhage, grade 3 or 4	210/969 (22)	224/955 (23)	0.93 (0.79–1.10)
Death or intraventricular hemorrhage, grade 3 or 4	291/984 (30)	290/976 (30)	1.0 (0.88–1.14)
Patent ductus arteriosus	459/990 (46)	487/984 (49)	0.93 (0.86–1.02)
Death or patent ductus arteriosus	556/990 (56)	582/984 (59)	0.95 (0.88–1.02)
Necrotizing enterocolitis	105/990 (11)	117/984 (12)	0.90 (0.70–1.14)
Death or necrotizing enterocolitis	269/990 (27)	268/984 (27)	1.00 (0.87–1.15)
Bronchopulmonary dysplasia at 36 wk postmenstrual age	327/799 (41)	383/797 (48)	0.86 (0.78–0.96)
Death or bronchopulmonary dysplasia at 36 wk postmenstrual age	506/978 (52)	559/973 (57)	0.90 (0.84–0.97)
Retinopathy of prematurity ≥stage 3§	153/802 (19)	160/798 (20)	0.98 (0.81–1.18)
Death or retinopathy of prematurity ≥stage 3	354/967 (37)	355/955 (37)	0.99 (0.89–1.10)
Late-onset sepsis	387/946 (41)	414/942 (44)	0.93 (0.84–1.04)
Death or late-onset sepsis	502/990 (51)	519/984 (53)	0.96 (0.89–1.04)

* Plus–minus values are means ±SD. The denominator used to calculate the percentage of infants with a specific outcome was the number of infants randomly assigned to each treatment group for whom that outcome was known at the time of hospital discharge, unless otherwise noted. These numbers of infants in the aggressive-phototherapy group and the conservative-phototherapy group were as follows: 781 and 755 for total serum bilirubin; 990 and 982 for daily total serum bilirubin, peak total serum bilirubin, and age at peak bilirubin; 498 and 511 for unbound bilirubin; 981 and 757 for age when phototherapy started (215 patients assigned to conservative phototherapy never received phototherapy); 923 and 954 for duration of phototherapy; 990 and 984 for exchange transfusions; 832 and 841 for days to regain birth weight; and 778 and 782 for length of hospital stay among survivors. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† The P value for the number of exchange transfusions was calculated with the use of Fisher's exact test, without adjustment for birth-weight stratum or center.

‡ The relative risk of each outcome was calculated for aggressive phototherapy as compared with conservative phototherapy. The P values were not significant except for bronchopulmonary dysplasia at 36 weeks of postmenstrual age and death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age, for which the P value was less than 0.05.

§ Retinopathy of prematurity was defined according to criteria of the International Committee for Classification of Retinopathy of Prematurity.

Table 3. Primary and Other Outcomes at 18 to 22 Months.*

Outcome	Aggressive Phototherapy	Conservative Phototherapy	Relative Risk (95% CI)†
	<i>no./total no. (%)</i>		
Death or neurodevelopmental impairment	465/902 (52)	493/902 (55)	0.94 (0.87–1.02)
Death‡	230/946 (24)	218/944 (23)	1.05 (0.90–1.22)
Neurodevelopmental impairment	235/902 (26)	275/902 (30)	0.86 (0.74–0.99)§
Profound impairment¶	80/895 (9)	119/896 (13)	0.68 (0.52–0.89)§
Death or profound impairment	310/895 (35)	337/896 (38)	0.92 (0.82–1.03)
Cerebral palsy			
Mild, moderate, or severe	81/929 (9)	91/924 (10)	0.89 (0.67–1.18)
Moderate or severe	38/929 (4)	53/923 (6)	0.71 (0.47–1.07)
Death or cerebral palsy			
Mild, moderate, or severe	311/929 (34)	309/924 (33)	1.00 (0.89–1.13)
Moderate or severe	268/929 (29)	271/923 (29)	0.99 (0.86–1.13)
Severe hearing loss	9/925 (1)	28/922 (3)	0.32 (0.15–0.68)§
Death or severe hearing loss	239/925 (26)	246/922 (27)	0.97 (0.84–1.12)
Blindness	2/928 (<1)	7/924 (1)	0.28 (0.06–1.37)
Death or blindness	232/928 (25)	225/924 (24)	1.03 (0.88–1.19)
Mental Developmental Index score <70	194/905 (21)	234/904 (26)	0.83 (0.71–0.98)§
Death or Mental Developmental Index score <70	424/905 (47)	452/904 (50)	0.94 (0.86–1.02)
Psychomotor Developmental Index score <70	127/898 (14)	152/894 (17)	0.84 (0.68–1.04)
Death or Psychomotor Developmental Index score <70	357/898 (40)	370/894 (41)	0.96 (0.86–1.06)
Mental Developmental Index score <85	380/905 (42)	429/904 (47)	0.89 (0.80–0.98)§
Death or Mental Developmental Index score <85	610/905 (67)	647/904 (72)	0.94 (0.89–1.00)§
Psychomotor Developmental Index score <85	262/898 (29)	299/894 (33)	0.88 (0.77–1.01)
Death or Psychomotor Developmental Index score <85	492/898 (55)	517/894 (58)	0.95 (0.88–1.03)
Athetosis	2/929 (<1)	10/923 (1)	0.20 (0.04–0.90)§
Death or athetosis	232/929 (25)	228/923 (25)	1.01 (0.87–1.17)
Seizures	29/933 (3)	28/925 (3)	1.03 (0.62–1.71)
Normal gross motor function	556/929 (60)	545/923 (59)	1.01 (0.94–1.08)
Ability to walk fluently**	544/929 (59)	529/924 (57)	1.02 (0.95–1.10)
Fine pincer grasp	606/929 (65)	582/922 (63)	1.03 (0.97–1.10)
Weight below 5th percentile for age	242/929 (26)	255/924 (28)	0.94 (0.81–1.10)
Fronto-occipital circumference below 5th percentile for age	120/929 (13)	128/922 (14)	0.93 (0.74–1.17)

* The denominator used to calculate the percentage of infants with a specific outcome was the number of infants randomly assigned to each treatment group for whom that outcome was known at 18 to 22 months. The Mental and Psychomotor Developmental Indexes are from the Bayley Scales of Infant Development II (on which scores can range from 50 to 150, with 150 indicating the most advanced development).

† The relative risk of each outcome was calculated for aggressive phototherapy as compared with conservative phototherapy.

‡ The mean (\pm SD) age at death was 57 \pm 98 days (range, 1 to 673) in the aggressive-phototherapy group and 52 \pm 88 days (range, 0 to 622) in the conservative-phototherapy group. The causes of death and the Kaplan–Meier survival estimates are shown in Table 1 and Figure 2 in the Supplementary Appendix.

§ $P < 0.05$.

¶ Infants with profound impairment included 22 with a Mental Developmental Index score of 50 and 121 with a score of less than 50.

|| Center was removed from the model owing to the absence of this rare outcome at several centers.

** The ability to walk fluently was defined as the ability to take 10 steps, unassisted, with a normal gait for the age.

Table 4. Secondary Analyses, According to Birth-Weight Stratum.*			
Outcome	Aggressive Phototherapy	Conservative Phototherapy	Relative Risk (95% CI)†
	<i>no./total no. (%)</i>		
Death or neurodevelopmental impairment			
501–750 g	272/405 (67)	270/403 (67)	1.00 (0.91–1.10)
751–1000 g	193/497 (39)	223/499 (45)	0.87 (0.75–1.01)
Death‡			
501–750 g	163/417 (39)	142/412 (34)	1.13 (0.96–1.34)
751–1000 g	67/529 (13)	76/532 (14)	0.90 (0.66–1.21)
Neurodevelopmental impairment			
501–750 g	109/405 (27)	128/403 (32)	0.86 (0.70–1.05)
751–1000 g	126/497 (25)	147/499 (29)	0.86 (0.71–1.05)
Death or profound impairment			
501–750 g	202/403 (50)	200/400 (50)	1.00 (0.88–1.14)
751–1000 g	108/492 (22)	137/496 (28)	0.79 (0.64–0.99)§
Profound impairment¶			
501–750 g	39/403 (10)	58/400 (14)	0.67 (0.46–0.98)§
751–1000 g	41/492 (8)	61/496 (12)	0.68 (0.47–0.99)§
Death or moderate or severe cerebral palsy			
501–750 g	181/410 (44)	169/408 (41)	1.06 (0.91–1.24)
751–1000 g	87/519 (17)	102/515 (20)	0.86 (0.66–1.11)
Moderate or severe cerebral palsy¶			
501–750 g	18/410 (4)	27/408 (7)	0.66 (0.37–1.19)
751–1000 g	20/519 (4)	26/515 (5)	0.76 (0.43–1.35)
Death or severe hearing loss			
501–750 g	167/408 (41)	152/407 (37)	1.09 (0.93–1.28)
751–1000 g	72/517 (14)	94/515 (18)	0.77 (0.58–1.02)
Severe hearing loss¶			
501–750 g	4/408 (1)	10/407 (2)	0.40 (0.13–1.26)
751–1000 g	5/517 (1)	18/515 (3)	0.28 (0.10–0.74)§
Death or Mental Development Index score <70			
501–750 g	251/405 (62)	253/402 (63)	0.98 (0.89–1.09)
751–1000 g	173/500 (35)	199/502 (40)	0.88 (0.75–1.03)
Mental Developmental Index score <70			
501–750 g	88/405 (22)	111/402 (28)	0.80 (0.63–1.01)
751–1000 g	106/500 (21)	123/502 (25)	0.87 (0.69–1.08)
Death or Psychomotor Developmental Index score <70			
501–750 g	227/404 (56)	218/399 (55)	1.03 (0.91–1.16)
751–1000 g	130/494 (26)	152/495 (31)	0.86 (0.71–1.05)
Psychomotor Developmental Index score <70¶			
501–750 g	64/404 (16)	76/399 (19)	0.83 (0.61–1.13)
751–1000 g	63/494 (13)	76/495 (15)	0.84 (0.62–1.14)

Table 4. (Continued.)

Outcome	Aggressive Phototherapy	Conservative Phototherapy	Relative Risk (95% CI) [†]
	no. (%)		
Death or Mental Developmental Index score <85			
501–750 g	315/405 (78)	326/402 (81)	0.96 (0.89–1.03)
751–1000 g	295/500 (59)	321/502 (64)	0.92 (0.84–1.02)
Mental Developmental Index score <85			
501–750 g	152/405 (38)	184/402 (46)	0.83 (0.71–0.98) [§]
751–1000 g	228/500 (46)	245/502 (49)	0.93 (0.82–1.06)
Psychomotor Developmental Index score <85			
501–750 g	117/404 (29)	130/399 (33)	0.91 (0.75–1.10)
751–1000 g	145/494 (29)	169/495 (34)	0.87 (0.73–1.03)
Athetosis [¶]			
501–750 g	1/410 (<1)	5/407 (1)	0.20 (0.02–1.69)
751–1000 g	1/519 (<1)	5/516 (1)	0.20 (0.02–1.70)

* The denominator used to calculate the percentage of infants with a specific outcome was the number of infants randomly assigned to each treatment group, and classified in each birth-weight subgroup, for whom that outcome was known at 18 to 22 months. The Mental and Psychomotor Developmental Indexes are from the Bayley Scales of Infant Development II (on which scores can range from 50 to 150, with 150 indicating the most advanced development).

[†] The relative risk of each outcome was calculated for aggressive phototherapy as compared with conservative phototherapy.

[‡] Among infants whose birth weight was 650 g or less, 106 of 214 (50%) died in the aggressive-phototherapy group, as compared with 80 of 212 (38%) in the conservative-phototherapy group (P=0.03).

[§] P<0.05.

[¶] Center was removed from the model owing to the absence of this rare outcome at several centers.

developmental impairment was lower with aggressive phototherapy than with conservative therapy (26% vs. 30%; relative risk, 0.86; 95% CI, 0.74 to 0.99; with 25 patients needing to be treated on average to prevent one case of impairment). In post hoc analyses, we found that this difference was almost entirely due to a reduction in profound impairment in the aggressive-phototherapy group (9%, vs. 13% in the conservative-phototherapy group; relative risk, 0.68; 95% CI, 0.52 to 0.89). As compared with the conservative-phototherapy group, the aggressive-phototherapy group also had significant reductions in the rate of severe hearing loss, in athetosis, and in Mental Developmental Index scores below 70 and below 85. However, aggressive phototherapy did not significantly reduce rates of death or combined outcomes including death or severe hearing loss, death or athetosis, or death or Mental Developmental Index scores below 70. Adjustment for the presence or absence of bronchopulmonary dysplasia had no material effect on the relative risks for the primary or secondary outcomes at 18 to 22 months.

Among the 1114 infants with a birth weight of 751 to 1000 g, aggressive phototherapy as compared with conservative phototherapy was associated with a marginally significant reduction in the rate of the primary outcome (relative risk, 0.87; 95% CI, 0.75 to 1.01) and significant reductions in the rates of severe hearing loss and, in post hoc analyses, profound neurodevelopmental impairment and the composite outcome of death or profound impairment at 18 to 22 months (Table 4). Other secondary outcomes listed were not significantly lower in the aggressive-phototherapy group.

Among the 860 infants with a birth weight of 501 to 750 g, the relative risk of death or neurodevelopmental impairment with aggressive phototherapy, as compared with conservative phototherapy, was 1.00 (95% CI, 0.91 to 1.10). In this subgroup, there was an increase of 5 percentage points in the rate of death and a decrease of 5 percentage points in neurodevelopmental impairment overall for aggressive phototherapy as compared with conservative phototherapy; in a post hoc analysis, there was a reduction of 4 per-

centage points in the rate of profound impairment (relative risk, 0.67; 95% CI, 0.46 to 0.98). The P value for the interaction of treatment group and birth-weight category was 0.15. Results of Bayesian analyses are shown in Figure 4 in the Supplementary Appendix; these analyses estimated an 89% probability that aggressive phototherapy increased the rate of death in this subgroup.

RELATIONSHIP OF SERUM BILIRUBIN AND OUTCOME

The mean (\pm SD) bilirubin level during the first 14 days among impaired survivors and unimpaired survivors was 5.4 ± 1.6 and 5.4 ± 1.5 mg per deciliter (92 ± 27 and 92 ± 26 μ mol per liter), respectively (P=0.45). Although the mean peak bilirubin level differed significantly between impaired survivors and unimpaired survivors (8.6 ± 2.3 vs. 8.3 ± 2.3 mg per deciliter [147 ± 39 vs. 142 ± 39 μ mol per liter], P=0.02), there was considerable overlap between the two groups in the peak values (Fig. 5 in the Supplementary Appendix). The mean bilirubin level among survivors with hearing loss as compared with those without hearing loss was 6.5 ± 1.7 versus 5.4 ± 1.5 mg per deciliter (111 ± 29 vs. 92 ± 26 μ mol per liter) (range, 2.7 to 11.9 vs. 0.6 to 10.1 [46 to 203 vs. 10 to 173]), respectively (P<0.001). The mean peak bilirubin level among survivors with hearing loss as compared with those without hearing loss was 10.5 ± 2.3 vs. 8.4 ± 2.3 mg per deciliter (180 ± 39 vs. 144 ± 39 μ mol per liter) (range, 5.8 to 17.8 vs. 1.3 to 17.7 [99 to 304 vs. 22 to 303]), respectively (P<0.001).

DISCUSSION

Decisions to use aggressive or conservative phototherapy in infants with extremely low birth weights have been based on inferences from observational studies relating bilirubin level to outcome.^{5-8,31} In this multicenter trial, we found no significant difference in the rate of death or neurodevelopmental impairment (the primary outcome) at 18 to 22 months of corrected age between neonates randomly assigned to receive aggressive phototherapy as compared with those assigned to receive conservative phototherapy. However, aggressive phototherapy significantly reduced the rate of neurodevelopmental impairment. In post hoc analyses, this reduction was attributable almost entirely to there being fewer infants with pro-

found impairment in the aggressive-phototherapy group.

In prespecified subgroup analyses, the rate of death among infants weighing 501 to 750 g at birth was higher, albeit not significantly so, with aggressive phototherapy than with conservative phototherapy. In this subgroup, the absolute increase in the number of deaths associated with aggressive phototherapy was 5 percentage points, a rate equal to the reduction of 5 percentage points in overall neurodevelopmental impairment and a reduction of slightly more than the 4 percentage points in profound impairment. The P value for the interaction between treatment group and birth weight (P=0.15) was not significant, but the power of the study was limited, and the possibility of an increase in the rate of death in the group with lower birth weights, as supported by the Bayesian analysis,^{28,29,32,33} should be taken seriously.³⁴

These findings are particularly worrisome because of the trend toward an increased rate of death in the only previous major trial assessing phototherapy for neonatal hyperbilirubinemia.¹⁴ In that trial, infants with a birth weight of less than 2500 g were randomly assigned to undergo either 96 hours of phototherapy or no phototherapy. The relative risk for death with phototherapy was 1.49 (95% CI, 0.93 to 2.40) among the 77 infants of extremely low birth weight and 1.32 (95% CI, 0.96 to 1.82) among the 1063 infants of low birth weight.¹⁷ Although subgroup analyses must be viewed with skepticism, they are most likely to be valid when, as in our study, they are supported by preexisting evidence, are unplanned, and are biologically plausible.^{35,36}

A reduction in the rate of death with conservative phototherapy might result from increased antioxidant levels¹² associated with higher bilirubin levels. Alternatively, a higher rate of death with aggressive phototherapy might result from oxidative injury to cell membranes.³⁷⁻³⁹ Such injury is particularly probable in the smallest, most immature infants whose gelatinous, thin skin readily transmits light.⁴⁰

The mechanism by which aggressive phototherapy would reduce the neurotoxic effects of bilirubin probably involves a reduction in the level of unbound bilirubin. The overlap in bilirubin values between infants with impairment and those without impairment and between those with severe hearing loss and those without it

provide little evidence to support a specific bilirubin threshold causing impairment. Longer follow-up is needed to assess effects of treatment on outcomes such as intelligence and executive function.

The reduced incidence of bronchopulmonary dysplasia in the aggressive-phototherapy group was not hypothesized, could have been a result of chance, and did not appear to explain the differences in outcome at 18 to 22 months. The number of days needed to regain birth weight was almost identical in the two groups, suggesting that differences in fluid management are unlikely to have caused a difference in the incidence of bronchopulmonary dysplasia.

The substantial reduction in overall neurodevelopmental impairment and profound impairment that we observed occurred with a reduction of only 2.8 mg per deciliter (48 μ mol per liter) in mean peak bilirubin level during the first 14 days. Greater reductions in bilirubin might further reduce impairment rates, providing the reductions could be safely achieved. Other treatment strategies, including the use of tin mesoporphyrin,⁴¹ also warrant evaluation to identify the safest and most effective strategies to address the postnatal rise in serum bilirubin level in infants of extremely low birth weight.

In summary, we found no significant effect of aggressive phototherapy as compared with

conservative phototherapy on the primary outcome of death or neurodevelopmental impairment in infants of extremely low birth weight, but the use of aggressive phototherapy significantly reduced the overall rate of neurodevelopmental impairment. Aggressive phototherapy may be preferred for infants with birth weights of 751 to 1000 g, because we found significant neurodevelopmental benefits in this subgroup and no evidence that the therapy increased the rate of death or other adverse outcomes at 18 to 22 months (including, in post hoc analyses, the rate of profound impairment). For infants with a birth weight of 501 to 750 g, the possibility that increased mortality may offset any potential benefits of aggressive phototherapy must be considered.

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APPENDIX

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