ORIGINAL ARTICLE

# Treatment of Neonatal Sepsis with Intravenous Immune Globulin

The INIS Collaborative Group*


## ABSTRACT

### BACKGROUND

Neonatal sepsis is a major cause of death and complications despite antibiotic treatment. Effective adjunctive treatments are needed. Newborn infants are relatively deficient in endogenous immunoglobulin. Meta-analyses of trials of intravenous immune globulin for suspected or proven neonatal sepsis suggest a reduced rate of death from any cause, but the trials have been small and have varied in quality.

### METHODS

At 113 hospitals in nine countries, we enrolled 3493 infants receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years.

### RESULTS

There was no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or nonmajor disability or of adverse events.

### CONCLUSIONS

Therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis. (Funded by the United Kingdom Medical Research Council and others; INIS Current Controlled Trials number, ISRCTN94984750.)


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Infection is a major cause of death in newborn infants.[1] Neonatal infection and inflammation are associated with serious complications, including brain damage and disability, particularly among preterm infants.[2-5] Polyvalent IgG immune globulin may help to prevent or treat infection, particularly in preterm infants, who have low serum IgG levels. Possible immunomodulatory mechanisms include enhancement of opsonic activity, complement activation, antibody-dependent cytotoxicity, improvement in neutrophil chemiluminescence,[6-8] and down-regulation of inflammatory cytokines.[9]

The potential benefits of intravenous immune globulin are supported by findings in several randomized trials. In a systematic review of 19 trials involving more than 5000 preterm or low-birthweight infants, the prophylactic use of intravenous immune globulin reduced the rate of late-onset infection by 3% with no significant reduction in the rates of death and adverse effects.[10] A systematic review of seven trials of adjunctive therapy with intravenous immune globulin involving 338 newborn infants of any gestational age who had suspected or proven sepsis showed no difference in mortality.[11] Two other systematic reviews[12,13] suggested that adjunctive therapy with intravenous immune globulin reduced mortality, but the evidence from one of these reviews[13] was judged to be unreliable because of study quality. The earlier review[12] recommended that intravenous immune globulin be used routinely in cases of proven sepsis, a conclusion that many observers might find premature. A systematic review of 14 randomized, controlled trials of therapy with intravenous immune globulin in 1450 adults with sepsis suggested a substantial reduction in mortality.[14] However, when the meta-analysis was restricted to 738 patients in four randomized, controlled trials of larger size or higher quality, the mortality reduction was lost, suggesting that the other trials might have been unrepresentative or biased. No trials of prophylaxis or therapy with intravenous immune globulin have assessed subsequent disability. We therefore designed a double-blind, randomized, controlled trial of adjunctive therapy with human nonspecific polyvalent IgG intravenous immune globulin, as compared with placebo, in newborn infants who had suspected or proven sepsis and who were receiving antibiotic therapy.

## Methods

### Study Design and Procedures

The study was conducted in accordance with the protocol for the International Neonatal Immunotherapy Study (INIS),[15] which is available with the full text of this article at NEJM.org, and was approved by each hospital's national and local research ethics committee. The trial was overseen by an independent steering committee with advice from an independent data and safety monitoring committee.

### Study Patients

Infants were eligible if they were receiving antibiotics for the treatment of proven or suspected serious infection with at least one of the following characteristics: a birth weight less than 1500 g; evidence of infection in blood culture, cerebrospinal fluid, or usually sterile body fluid; or need for respiratory support through an endotracheal tube. Exclusion criteria were previous administration of intravenous immune globulin and a decision by clinical staff that intravenous immune globulin was either definitely needed or contraindicated (e.g., because of a severe congenital abnormality or a contraindication according to the manufacturer's product information sheet).

Written informed consent was obtained from a parent. Infants were randomly assigned in a blinded fashion to receive either intravenous immune globulin or placebo. In Europe and Argentina, neonatal staff opened the next sequentially numbered study pack, which was stored in the neonatal unit and contained all materials necessary to administer a course of the study drug. The assignment sequence was generated by the National Perinatal Epidemiology Unit in Oxford, United Kingdom, with balance within random block sizes of 2 to 8. In Australia and New Zealand, the hospital pharmacy was contacted, and the next assignment was taken from a randomization list generated by the National Health and Medical Research Council Clinical Trials Centre in Sydney.

### Clinical Management

In the group receiving intravenous immune globulin, an intravenous infusion of immune globulin at a dose of 500 mg (10 ml) per kilogram of body

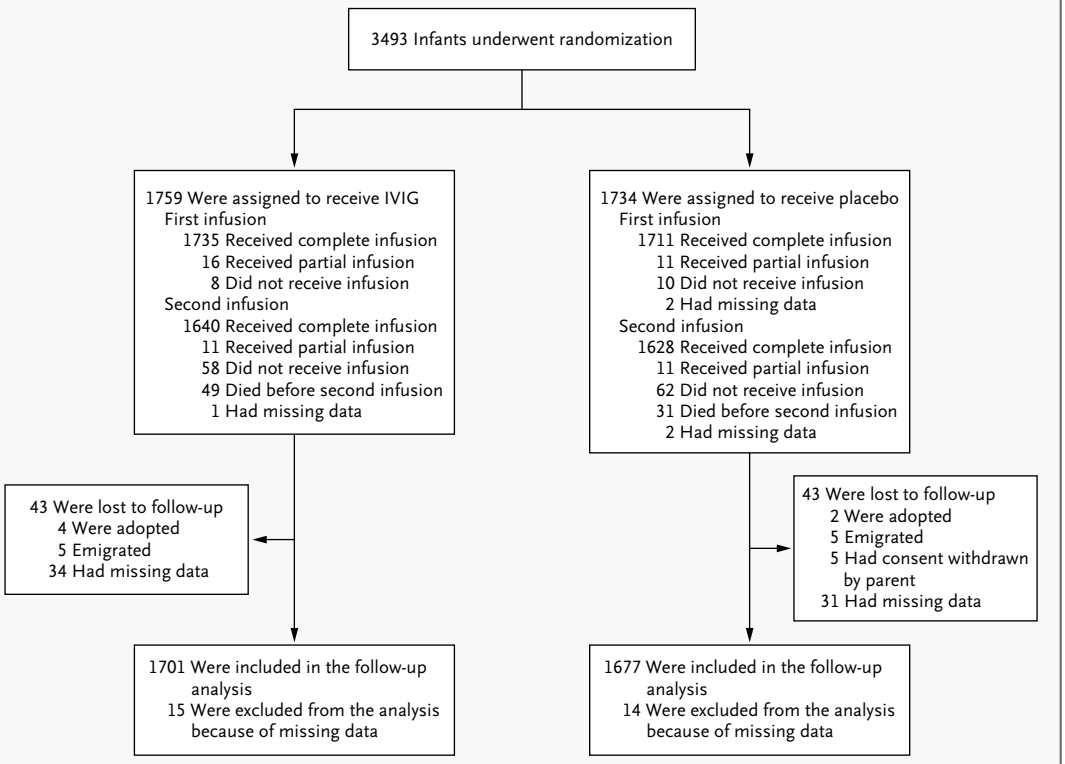


**Figure 1. Enrollment and Outcomes.**
IVIG denotes intravenous immune globulin.

weight was administered and repeated after 48 hours. In Europe and Argentina, intravenous immune globulin and placebo were produced by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service. In Australia and New Zealand, the intravenous immune globulin preparation was Intragam P (CSL).

In the control group, intravenous infusion of an identical volume of placebo was administered and repeated after 48 hours. In Europe and Argentina, the active drug and placebo were reconstituted by clinical staff by mixing normal saline with freeze-dried plugs of study product. Placebo was 0.2% albumin solution in normal saline. The two infusions looked identical, were colorless, and frothed on agitation. In Australia and New Zealand, the pharmacy made up either Intragam P or a placebo solution (normal saline). Syringes and tubing were masked with yellow tape.

The intravenous immune globulin or placebo was infused according to the manufacturer's instructions over a period of 4 to 6 hours. No further intravenous immune globulin or placebo could be given after the administration of the two doses. Other aspects of management were left to the pediatrician responsible for the infant's care.

### PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the rate of death or major disability at the age of 2 years, with adjustment for gestational age. Major disability was assessed by means of questionnaires sent to the child's parents and health care professionals. Major disability was defined according to prespecified criteria[16,17] in the following domains: neuromotor function, seizures, auditory function, communication, visual function, cognitive function, and other physical disability. The instruments for measuring disability[17,18] are described in the protocol.[15] Cognitive function was assessed on the basis of parental reports with the use of the Parent Report of Children's Abilities–Revised (PARCA-R).[18] A PARCA-R Parent Report

Composite (PRC) score of less than 31 (on a scale of 0 to 158, with higher scores indicating higher cognitive function) was used to identify cases of major cognitive delay. The cutoff point was based on the results of a validation substudy of INIS that evaluated the PARCA-R against the well-established Bayley II Mental Development Index (MDI),[19] with the standard for major cognitive delay being an MDI score that was less than 3 SD below the population norm. (Details are provided in the Supplementary Appendix, available at NEJM.org.) We explored the effect of using other PRC cutoff points (Table S2 in the Supplementary Appendix). The criteria for major disability are also described in the Supplementary Appendix.

Secondary short-term outcomes were the rates of death before hospital discharge, chronic lung disease (defined as oxygen dependency 28 days

**Table 1. Baseline Characteristics of the Infants.***

| Characteristic | Intravenous Immune Globulin (N=1759) | Placebo (N=1734) |
|---|---|---|
| Birth weight — g | | |
| Median | 1009 | 1000 |
| Interquartile range | 778–1426 | 770–1460 |
| Age at randomization — hr | | |
| Median | 204 | 204 |
| Interquartile range | 74–408 | 74–399 |
| Male sex — no. (%) | 993 (56.5) | 1007 (58.1) |
| Gestational age at birth — wk | | |
| Median | 28 | 28 |
| Interquartile range | 26–31 | 26–31 |
| Evidence of infection in blood culture, cerebrospinal fluid, or normally sterile body fluid — no. (%)† | | |
| Any site | 739 (42.0) | 728 (42.0) |
| Blood | 694 (39.5) | 677 (39.0) |
| Cerebrospinal fluid | 91 (5.2) | 72 (4.2) |
| Other site | 26 (1.5) | 36 (2.1) |
| Cause of infection | | |
| No. of infants evaluated | 739 | 728 |
| Early-onset infection — no. (%) | | |
| Group B streptococcus | 19 (2.6) | 13 (1.8) |
| Other pathogen | 25 (3.4) | 35 (4.8) |
| Indeterminate cause | 1 (0.1) | 4 (0.5) |
| Late-onset infection — no. (%) | | |
| Coagulase-negative staphylococcus | 297 (40.2) | 286 (39.3) |
| Gram-positive organism except coagulase-negative staphylococcus | 169 (22.9) | 160 (22.0) |
| Gram-negative organism | 148 (20.0) | 145 (19.9) |
| Fungal infection | 17 (2.3) | 24 (3.3) |
| Other pathogen | 5 (0.7) | 5 (0.7) |
| Indeterminate cause | 14 (1.9) | 16 (2.2) |
| >1 Type of infection | 43 (5.8) | 40 (5.5) |
| Bowel perforation or definite necrotizing enterocolitis — no. (%) | 124 (7.0) | 125 (7.2) |
| Surgery in previous 7 days — no. (%) | 55 (3.1) | 59 (3.4) |

**Table 1. (Continued.)**

| Characteristic | Intravenous Immune Globulin (N=1759) | Placebo (N=1734) |
|---|---|---|
| Respiratory support through endotracheal tube — no. (%) | 1136 (64.6) | 1126 (64.9) |
| Risk of death — no. (%)‡ | | |
| High | 304 (17.3) | 299 (17.2) |
| Intermediate | 1071 (60.9) | 1022 (58.9) |
| Other | 384 (21.8) | 413 (23.8) |
| Maternal clinical chorioamnionitis — no. (%) | | |
| Patients with condition | 251 (14.3) | 277 (16.0) |
| Missing data | 261 (14.8) | 256 (14.8) |
| Elevated maternal C-reactive protein, >80 mg/liter — no. (%) | | |
| Yes | 38 (2.2) | 47 (2.7) |
| Not measured | 1129 (64.2) | 1116 (64.4) |
| Missing data | 330 (18.8) | 333 (19.2) |
| Duration of membrane rupture — no. (%) | | |
| <24 hr | 1007 (57.2) | 992 (57.2) |
| 24–48 hr | 57 (3.2) | 45 (2.6) |
| >48 hr | 291 (16.5) | 297 (17.1) |
| Missing data | 404 (23.0) | 400 (23.1) |
| Source of intravenous immune globulin or placebo — no. (%) | | |
| United Kingdom, Europe, or Argentina | 1062 (60.4) | 1033 (59.6) |
| Australia or New Zealand | 697 (39.6) | 701 (40.4) |

* There were no significant differences between the two groups. Data regarding age were missing for 14 infants receiving intravenous immune globulin and 12 receiving placebo. Some data regarding maternal clinical chorioamnionitis, maternal C-reactive protein, and duration of membrane rupture were missing because these data were not collected during the early stages of the trial.

† Infants could have more than one site of infection.

‡ Criteria for the determination of risk of death are provided in the subgroup-analyses section in the study protocol, available at NEJM.org. "Other" risk of death includes reasons that did not satisfy criteria for high or intermediate risk according to the protocol.

after birth), major cerebral abnormality, relevant positive culture after trial entry (and causative organisms), pneumonia, and necrotizing enterocolitis, along with the length of hospital stay. Secondary long-term outcomes (at 2 years with adjustment for gestational age) were the rates of death and major and nonmajor disability.

### STUDY OVERSIGHT

The trial was designed by the INIS coinvestigators. The data were collected and checked for completeness and accuracy by the National Perinatal Epidemiology Unit and by the Sydney Clinical Trials Unit. The data were analyzed by the National Perinatal Epidemiology Unit. The study drug was purchased with the use of funds from study grants, and the manufacturers had no role in the trial design, conduct, or analysis. The manuscript was written by the INIS writing committee with input from the coinvestigators. The writing committee, on behalf of the INIS Study Collaborative Group, vouches for the accuracy and completeness of this report and for the fidelity of the report to the study protocol.

### STATISTICAL ANALYSIS

The original sample-size estimate was based on a range of rates for the primary outcome because no reliable data were available. The threshold of disease severity at which clinicians would recruit infants was unknown, and there were no estimates regarding rates of later disability. We determined that the enrollment of 5000 infants and event rates

between 15 and 30% would provide a power of 90% to determine a relative reduction in the risk of death or major disability of 14 to 25%.

Demographic and clinical data were summarized with counts and percentages for categorical variables, means (±SD) for normally distributed continuous variables, and medians (with interquartile or simple ranges) for other continuous variables. We analyzed all data according to the assigned groups, regardless of any deviation from the protocol. Disability outcomes are presented for infants who survived and for whom follow-up data were available.

Comparative analysis entailed calculating the relative risk plus 95% confidence interval for dichotomous outcomes, the mean difference (plus 95% confidence interval) for normally distributed continuous outcomes, and the median difference (plus 95% confidence interval) for skewed continuous variables. To account for the number of comparisons, 99% confidence intervals were used for subgroup analyses. Reported P values are two-sided without adjustment, and a P value of less than 0.05 was considered to indicate statistical significance (0.01 for subgroup analyses).

We conducted prespecified subgroup analyses for the primary outcome according to the following variables: weight (<1500 g vs. ≥1500 g), size for gestational age (<10th vs. ≥10th percentile), gestational age at birth (<26 weeks, 26 to 27 weeks, 28 to 29 weeks, or ≥30 weeks), male versus female sex, the presence or absence of maternal chorioamnionitis, maternal C-reactive protein level (≤80 mg per liter [normal] vs. >80 mg per liter [elevated]), the duration of membrane rupture (<24 hours, 24 to <48 hours, and ≥48 hours), risk of death (see detailed definition in the Supplementary Appendix), type of infection (early onset, late

**Table 2. Main Study Outcomes.***

| Outcome | Intravenous Immune Globulin | Placebo | Relative Risk (95% CI)† |
|---|---|---|---|
| **Primary outcome** | | | |
| Death or major disability at 2 yr — no./total no. (%)‡ | 686/1759 (39.0) | 677/1734 (39.0) | 1.00 (0.92–1.08) |
| **Secondary outcomes** | | | |
| Death at 2 yr — no./total no. (%) | 322/1759 (18.3) | 306/1734 (17.6) | 1.04 (0.90–1.20) |
| Disability at 2 yr — no./total no. (%)‡ | | | |
| Major | 364/1437 (25.3) | 371/1428 (26.0) | 0.98 (0.86–1.10) |
| Nonmajor | 480/1437 (33.4) | 470/1428 (32.9) | |
| None | 535/1437 (37.2) | 530/1428 (37.1) | |
| Death in hospital — no./total no. (%) | 292/1759 (16.6) | 287/1734 (16.6) | 1.00 (0.86–1.16) |
| Use of supplemental oxygen on day 28 — no./total no. (%)§ | 779/1394 (55.9) | 794/1391 (57.1) | 0.98 (0.92–1.04) |
| Major cerebral abnormality — no./total no. (%) | 234/1759 (13.3) | 201/1734 (11.6) | 1.15 (0.96–1.37) |
| Confirmed sepsis after trial entry — no./total no. (%) | 461/1759 (26.2) | 458/1734 (26.4) | 0.99 (0.89–1.11) |
| Any | 461/1759 (26.2) | 458/1734 (26.4) | 0.99 (0.89–1.11) |
| 1 episode | 332/461 (72.0) | 321/458 (70.1) | |
| ≥2 episodes | 129/461 (28.0) | 137/458 (29.9) | |
| Cause of confirmed sepsis — no./total no. (%)¶ | | | |
| Gram-positive organism except coagulase-negative staphylococcus | 97/461 (21.0) | 103/458 (22.5) | |
| Coagulase-negative staphylococcus | 302/461 (65.5) | 281/458 (61.4) | |
| Gram-negative organism | 100/461 (21.7) | 121/458 (26.4) | |
| Fungal organism | 43/461 (9.3) | 46/458 (10.0) | |
| Other pathogen | 17/461 (3.7) | 19/458 (4.1) | |
| Indeterminate cause | 23/461 (5.0) | 14/458 (3.1) | |

**Table 2. (Continued.)***

| Outcome | Intravenous Immune Globulin | Placebo | Relative Risk (95% CI)† |
|---|---|---|---|
| Pneumonia — no./total no. (%) | 224/1759 (12.7) | 221/1734 (12.7) | 1.00 (0.84–1.19) |
| Necrotizing enterocolitis — no./total no. (%) | | | |
| New episode‖ | 132/1759 (7.5) | 120/1734 (6.9) | 1.08 (0.85–1.37) |
| With bowel perforation or definite necrotizing enterocolitis at trial entry | 17/1759 (1.0) | 10/1734 (0.6) | |
| Infants discharged home from hospital | | | |
| Total no. | 1467 | 1445 | |
| Duration of hospital stay — days | | | |
| Median | 64 | 64 | NA |
| Interquartile range | 37–92 | 37–93 | |

* Data were missing for infants in the following categories: major disability component of the primary outcome at 2 years, 58 infants receiving intravenous immune globulin and 57 infants receiving placebo; major cerebral abnormality, 2 infants receiving intravenous immune globulin and 5 infants receiving placebo; pneumonia, 1 infant receiving intravenous immune globulin and 5 infants receiving placebo; necrotizing enterocolitis, 2 infants receiving intravenous immune globulin and 4 infants receiving placebo; and duration of hospital stay, 7 infants receiving intravenous immune globulin and 4 infants receiving placebo. NA denotes not applicable.

† Values are the relative risk among infants receiving intravenous immune globulin, as compared with those receiving placebo. Values for infants with missing data were excluded from the denominator in the calculation of relative risk. Premature infants were evaluated at 2 years of age as if they had been born at term.

‡ The classifications of major and nonmajor disability were based on the criteria of the National Perinatal Epidemiology Unit.[17] Children meeting the criteria for severe disability in any of the domains of neuromotor function, seizures, auditory function, communication, visual function, cognitive function, or other physical disability were regarded as having a major disability. Those meeting the criteria for disability (but not severe disability) were classified as having a nonmajor disability.

§ Infants who died before 28 days (179 receiving intravenous immune globulin and 157 receiving placebo) or who were recruited after 28 days (186 receiving intravenous immune globulin and 186 receiving placebo) were excluded from the calculation of the relative risk of oxygen dependency at 28 days. In addition, data were missing in this category for 28 infants receiving intravenous immune globulin and 4 infants receiving placebo.

¶ Infants could have more than one type of sepsis.

‖ Confirmation that an episode of necrotizing enterocolitis was new could not be obtained for 8 infants receiving intravenous immune globulin and 4 infants receiving placebo.

onset, or onset after surgery), and the source of intravenous immune globulin or placebo (Europe or Argentina vs. Australia or New Zealand).

After a meeting of the independent data and safety monitoring committee in December 2005, when data for 2003 infants had been analyzed, the trial steering committee was advised that the primary outcome was substantially more frequent than estimated in the protocol and that an enrollment of 3500 infants would provide a power of 90% to determine a relative risk reduction of 14%. This new sample-size target was adopted.

## RESULTS

### PATIENTS

From October 2001 through September 2007, a total of 3493 infants were recruited from 113 hospitals: 1454 infants from the United Kingdom, 1043 from Australia, 480 from Argentina, 355 from New Zealand, 52 from Serbia, 42 from Greece, 33 from Denmark, 20 from Belgium, and 14 from Ireland (Fig. 1). Infant and maternal characteristics were very similar in the two study groups (Table 1). On review, it was determined that 23 infants (0.7%) (11 who were assigned to receive intravenous immune globulin and 12 who were assigned to receive placebo) were not eligible for participation in the study. Data from these infants were included in the intention-to-treat analysis, and the removal of their data did not significantly alter the results.

A total of 98.3% of the infants received a first full infusion, and 93.5% received a second full infusion; 2.3% of the infants died between the first infusion and the scheduled second infusion (for details, see the Supplementary Appendix). Only

18 infants (0.5%) were known not to have received any assigned intervention.

### PRIMARY AND SECONDARY OUTCOMES

In the group receiving intravenous immune globulin, 686 of 1759 infants (39.0%) either died or had major disability at the age of 2 years, as compared with 677 of 1734 infants (39.0%) in the placebo group (relative risk, 1.00; 95% confidence interval [CI], 0.92 to 1.08) (Table 2, and Fig. S1 in the Supplementary Appendix). This result was unaltered by varying the cutoff point used to define major disability for the cognitive domain (see the Supplementary Appendix).

Similarly, there were no significant between-group differences for any secondary outcome, including rates of subsequent episodes of sepsis and causative organisms (Table 2). In survivors at 2 years, there were no significant differences in the rates of either major or nonmajor disability. Although the development of cerebral palsy was not a prespecified outcome, there was no significant difference in the proportions of children with this diagnosis at 2 years: 122 of 1437 patients (8.5%) receiving intravenous immune globulin and 118 of 1428 patients (8.3%) receiving placebo. In the subgroup analyses of the primary outcome, there was no evidence that the outcomes with intravenous immune globulin differed significantly from those with placebo in any prespecified subgroup (Fig. 2).

### ADVERSE EVENTS

A total of 22 adverse events were reported, 12 in the group receiving intravenous immune globulin (including 2 deaths) and 10 in the placebo group (including 4 deaths) (Table S5 in the Supplementary Appendix).

## DISCUSSION

In this trial, we found no difference in the primary outcome of death or major disability at 2 years of age among 3493 infants with suspected or proven neonatal sepsis who received either intravenous immune globulin or placebo during a 48-hour period. Similarly, there was no between-group difference in the individual components of the primary outcome or in seven other prespecified secondary outcomes, nor was there evidence of benefit or harm in 28 preplanned subgroup analyses according to risk factors for disease severity. These results clearly show that intravenous immune globulin, as prescribed in this trial, did not achieve the moderate improvements in outcome that were postulated. A larger trial would be necessary to show even smaller differences.[20]

We were unable to accurately determine the proportion of eligible infants who were recruited to participate in the trial. Infants were eligible if they were judged to have serious suspected or proven infection, and thresholds for study entry varied according to the center and the individual clinician, particularly since microbiologic evidence was not required. Indeed, waiting for microbiologic confirmation might have been inappropriate if there had been a chance that treatment with intravenous immune globulin at the onset of suspected sepsis could be effective.

A Cochrane review of intravenous immune globulin for infection in neonates with suspected or subsequently proven infection included 10 trials of variable quality undertaken in eight countries.[13] Mortality was reduced among patients with clinically suspected infection in 7 trials involving 378 infants (relative risk, 0.58; 95% CI, 0.38 to 0.89) and among patients with subsequently proven infection in 7 trials involving 262 patients (relative risk, 0.55; 95% CI, 0.31 to 0.98). In our study, we did not find any discernible benefit of therapy with intravenous immune globulin for suspected sepsis (in 3493 infants) or subsequently proven sepsis (in 1461 infants).

Our study was similar to the earlier trials with respect to the dose of intravenous immune globulin used and the characteristics of the infants at the time of presentation with clinical sepsis. Compliance with the protocol was very high. The inclusion criteria were broad enough to include all groups of infants for whom a benefit of treatment might be hypothesized. The prespecified subgroup analyses included larger numbers of neonates than the existing meta-analyses of all neonatal data.

In three of the earlier trials, infants received a preparation of intravenous immune globulin that was enriched with IgM,[21-23] so it might be argued that our study did not exclude a benefit with enriched immune globulin preparations. However, these three trials were small, and two of them were not randomized, placebo-controlled, or blinded. Four trials either did not use a placebo or were not blinded,[21,23-25] and two were not randomized,[21,26] so a key reason for the difference between our

| Subgroup | IVIG | Placebo | Relative Risk (99% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no.* | | | |
| Birth weight | | | | 0.14 |
| <1500 g | 552/1309 | 558/1279 | 0.97 (0.86–1.09) | |
| ≥1500 g | 134/392 | 119/398 | 1.14 (0.87–1.49) | |
| Size for gestational age | | | | 0.97 |
| <10th percentile | 186/365 | 196/387 | 1.01 (0.84–1.21) | |
| ≥10th percentile | 498/1334 | 480/1289 | 1.00 (0.88–1.14) | |
| Gestational age at birth | | | | 0.56 |
| <26 wk | 234/427 | 197/392 | 1.09 (0.92–1.30) | |
| 26–27 wk | 164/435 | 190/442 | 0.88 (0.71–1.08) | |
| 28–29 wk | 105/311 | 124/305 | 0.83 (0.63–1.09) | |
| ≥30 wk | 183/528 | 166/538 | 1.12 (0.90–1.41) | |
| Sex | | | | 0.72 |
| Male | 422/964 | 421/975 | 1.01 (0.89–1.16) | |
| Female | 264/757 | 256/702 | 0.98 (0.82–1.18) | |
| Maternal chorioamnionitis | | | | 0.12 |
| <30 wk with chorioamnionitis | 80/197 | 95/215 | 0.92 (0.68–1.24) | |
| <30 wk without chorioamnionitis | 316/777 | 333/742 | 0.91 (0.78–1.06) | |
| ≥30 wk | 183/528 | 166/538 | 1.12 (0.90–1.41) | |
| Elevated maternal CRP (>80 mg/liter) | | | | 0.63 |
| <30 wk with elevated CRP | 13/30 | 15/39 | 1.13 (0.53–2.38) | |
| <30 wk without elevated CRP | 75/213 | 69/189 | 0.96 (0.68–1.36) | |
| ≥30 wk | 183/528 | 166/538 | 1.12 (0.90–1.41) | |
| Membrane rupture | | | | 0.29 |
| <37 wk with membrane rupture ≥48 hr | 104/277 | 113/283 | 0.94 (0.71–1.24) | |
| <37 wk with membrane rupture 24 to <48 hr | 14/53 | 16/35 | 0.58 (0.27–1.23) | |
| <37 wk with membrane rupture <24 hr | 353/852 | 346/838 | 1.00 (0.86–1.16) | |
| ≥37 wk | 43/150 | 44/163 | 1.06 (0.66–1.70) | |
| Risk of death | | | | 0.12 |
| High | 195/294 | 173/294 | 1.13 (0.96–1.33) | |
| Intermediate | 365/1035 | 367/988 | 0.95 (0.82–1.11) | |
| Other | 126/372 | 137/395 | 0.98 (0.75–1.26) | |
| Type of infection | | | | 0.22 |
| Early onset | 21/45 | 14/50 | 1.67 (0.82–3.40) | |
| Late onset | 250/646 | 237/624 | 1.02 (0.85–1.22) | |
| After surgery | 13/22 | 16/27 | 1.00 (0.54–1.84) | |
| Source of IVIG or placebo | | | | 0.27 |
| UK, Europe, or Argentina | 464/1023 | 440/1001 | 1.03 (0.91–1.17) | |
| Australia or New Zealand | 222/678 | 237/676 | 0.93 (0.77–1.14) | |

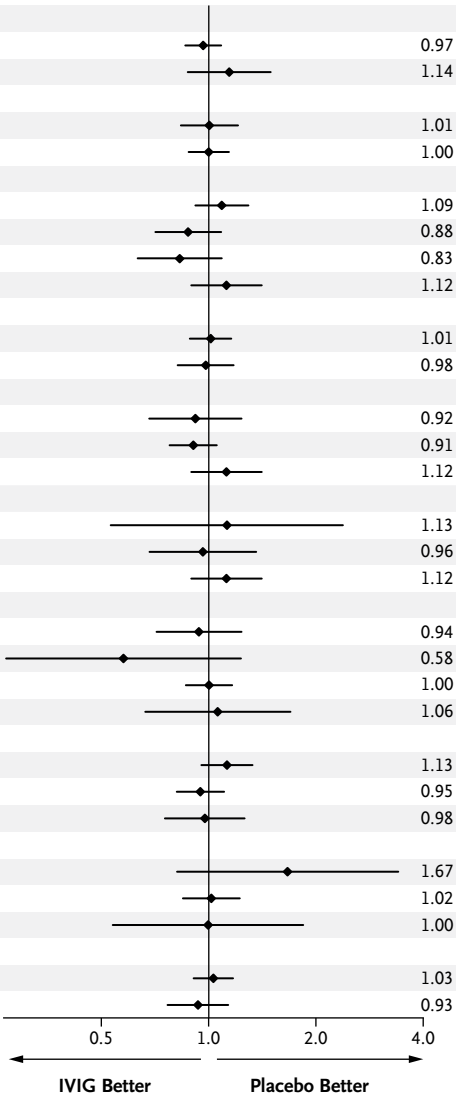


**Figure 2. Subgroup Analyses of Rates of Death or Major Disability at 2 Years of Age (Primary Outcome).**

The P value for the gestational age at birth was calculated by means of the chi-square test for trend. CRP denotes C-reactive protein, IVIG intravenous immune globulin, and UK United Kingdom.

findings and those of earlier studies is likely to be the weaknesses in the designs of the earlier trials. This hypothesis is consistent with the results of a meta-analysis of 14 studies (of varying quality) of intravenous immune globulin in adults with severe sepsis, which showed a significant reduction in mortality. However, the largest trial showed no benefit, and when the analysis was restricted to this study and three others of higher quality, the odds ratio for death was 0.96 (95% CI, 0.71 to 1.3).[14] It is important to emphasize that the findings from meta-analyses should be interpreted with caution when the underlying evidence is of variable quality.

An important feature of our study was its assessment of later disability as well as early mortality. Information about the outcome at 2 years was available for 97% of surviving infants. We used

an accepted standard[17] to define major disability and parental reports of children's development to assess cognitive ability because of the large numbers of children involved. The evaluation instrument that we chose, the PARCA-R, had been well validated in comparison with the Bayley II scale, and at the time the trial was initiated, we knew of ongoing work to further validate this measure in preterm survivors. However, for the cutoff points that capture the relatively small proportion of children with major disability, the existing validation work is based on a very small number of children (164). We therefore chose to use part of the trial population, before unblinding or analysis according to study-group assignment, to derive cutoff points for major and nonmajor disability, which we then used for the whole trial population. Sensitivity analyses that used the previously reported cutoff points did not show a significant effect on the study's conclusions (see the Supplementary Appendix). Although measures with better external validation are preferable for comparing children's development, the use of other approaches in randomized trials does not affect the internal validity of the comparison. In view of the relatively limited evidence to support a cutoff point of 44 on the PARCA-R to define severe cognitive disability, we considered our approach to represent a more accurate measure of the proportion of children with a major disability, since this analysis was based on data from 485 children.

On the basis of the established role of intravenous immune globulin in modifying the course of inflammatory conditions of the central nervous system in adults, we hypothesized that the immunomodulatory effects of intravenous immune globulin might extend to inflammatory injury in the developing brain or lungs.[9] There was no significant between-group difference in any measure of central nervous system function, even when the analysis was restricted to preterm infants who were enrolled between 26 and 29 weeks of gestation. In this subgroup analysis, the absolute between-group difference in the risk of major disability was 6 percentage points, but the 99% confidence intervals included zero. Approximately two thirds of all neonates who were enrolled in the trial had a gestational age of less than 30 weeks at birth, and no significant difference was seen between the groups in the rates of oxygen dependency at 28 days.

In conclusion, we found that the use of polyvalent IgG immune globulin was not associated with significant differences in the risk of major complications or other adverse outcomes in neonates with suspected or proven sepsis. The prophylaxis and treatment of neonatal sepsis remain a major global priority,[1] and there is a need to step up the testing of promising interventions in large international trials.[27]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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