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ORIGINAL ARTICLE

Treatment of Neonatal Sepsis with Intravenous Immune Globulin

The INIS Collaborative Group*

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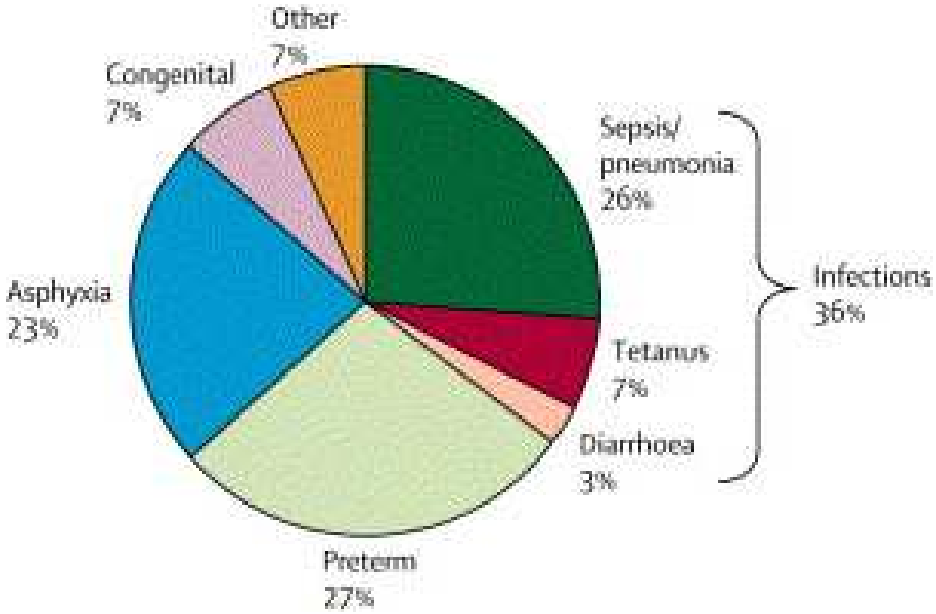
Background

- In the year 2000, there were 4 million neonatal deaths worldwide



- Lancet. 2005 Mar 5-11;365(9462):891-900.

Background

- Neonatal infection and inflammation are associated with serious complications such as brain damage and disability particularly in preterm infants
- Polyvalent IgG immune globulin may help to prevent or treat infection particularly in preterm infants, who have low serum IgG levels

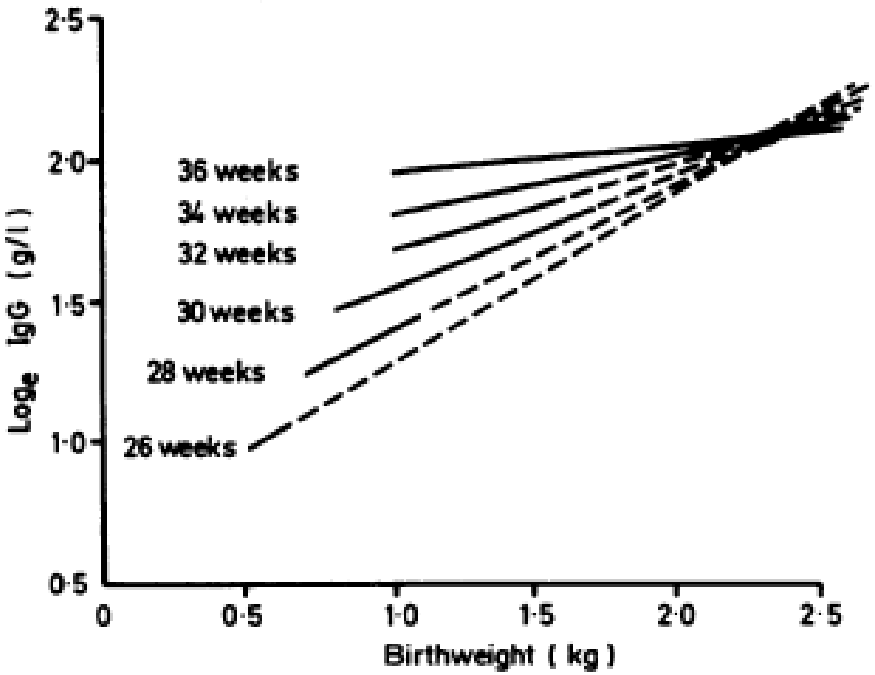


Fig. 1 *IgG (log$_e$ g/l) against birthweight (X_2) and gestational age (X_1).*

The regression equation:
$\text{Log}_e\ (\text{IgG}) = 2{\cdot}084 - 0{\cdot}0535(X_1 - 37{\cdot}58)\ (X_2 - 2{\cdot}318)$ is illustrated by log$_e$ (IgG) *v* birthweight at stated gestational ages, with the solid lines covering the range of data studied.

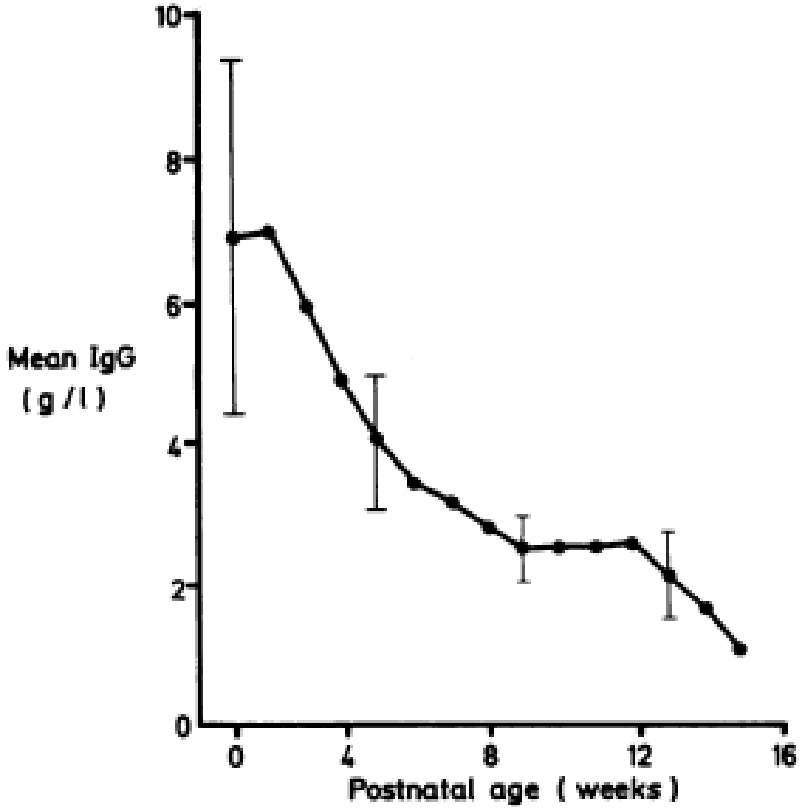


Fig. 3 *Change in IgG value with age.*

Regression equation $\log_e\ (\text{IgG}) = a_n - 0{\cdot}0898$ age. ($\bar{\text{I}}$ = ISD).

IgG values at birth ranged from 260 mg/dL to 1440 mg/dL
(median 600-700 mg/dL)

S P Conway, P R Dear, and I Smith. Immunoglobulin profile of the preterm baby. Arch Dis Child. 1985 March; 60(3): 208–212.

Background

- Possible immunomodulating mechanism
  - Enhancement of opsonic activity
  - Complement activation
  - Antibody-dependent cytotoxicity
  - Improvement in neutrophil chemiluminescence
  - Down-regulation of inflammatory cytokines

6. Baley JE. Neonatal sepsis: the potential for immunotherapy. Clin Perinatol 1988;15:755-71.
7. Melvan JN, Bagby GJ, Welsh DA, Nelson S, Zhang P. Neonatal sepsis and neutrophil insufficiencies. Int Rev Immunol 2010;29:315-48.
8. Christensen RD, Brown MS, Hall DC, Lassiter HA, Hill HR. Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. J Pediatr 1991;118:606-14.
9. Mohan PV, Tarnow-Mordi W, Stenson B. Can polyclonal intravenous immunoglobulin (IVIG) limit cytokine mediated cerebral damage and chronic lung disease in preterm infants? Arch Dis Child Fetal Neonatal Ed 2004;89:F5-F8.

Background

- 2002 systematic review of 7 trials of adjunctive therapy with IVIG involving 338 newborn infants of any gestational age who had suspected or proven sepsis showed no difference in mortality

- Cochrane Database Syst Rev 2002; 1:CD001090

Background

- 2004 systematic review of 19 trials involving more than 5000 preterm or low-birth weight infants
- Prophylactic use of IVIG reduced the rate of late-onset infection by 3% with no significant reduction in the rates of death and adverse effects

- Cochrane Database Syst Rev 2004;1: CD000361.

Background

- 2 other systematic reviews suggested that adjunctive therapy with IVIG reduced mortality
- A 1998 review recommended use of IVIG routinely in cases of proven sepsis “a conclusion that many observers might find premature”

- Semin Perinatol 1998;22:50-63.

Background

- Cochrane 2010 review looking at 10 trials of varying quality on the use of IVIG for suspected or subsequently proven infection in neonates
- Mortality reduced among patients with clinically suspected infection in 7 trials involving 378 infants (RR 0.58; 95%CI 0.38 to 0.89)
- Mortality reduced in pts with subsequently proven infection in 7 trials involving 262 patients (RR 0.55; 95% CI 0.31 to 0.98)

- Cochrane Database Syst Rev 2010;3:CD001239

Background

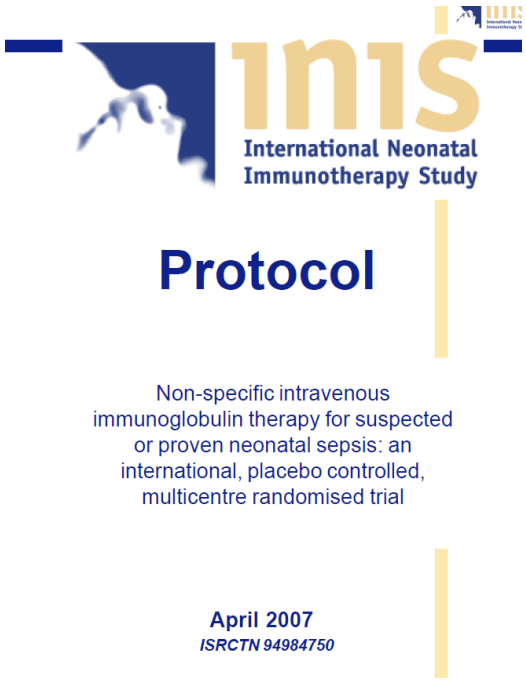
- Systematic review of 14 randomized, controlled trials of therapy with IVIG in 1450 adults with sepsis suggested a substantial reduction in mortality
- When meta-analysis restricted to 738 patients in the 4 randomized, controlled trials of larger size or higher quality, the mortality reduction was LOST
- Crit Care Med 2007;35:2686-92.

Objective

- No trials of prophylaxis or therapy with IVIG have assessed subsequent disability
- This is a double-blind, randomized, placebo-controlled trial of adjunctive therapy with human nonspecific polyvalent IgG intravenous immunoglobulin in newborn infants who had suspected or proven sepsis and who were receiving antibiotic therapy

Study Design

- In accordance with the protocol for the International Neonatal Immunotherapy Study (INIS)
- Europe, Argentina, Australia, New Zealand
- Study drug purchased with fund from study grants
- Manufacturers had no role in trial design, conduct or analysis



Study Patients

- Inclusion criteria
  - Neonate receiving antibiotics for tx of proven or suspected serious infection with at least one of the following characteristics
    - Birth weight <1500g (3.3 lbs)
    - Evidence of infection in blood culture, csf, or usually sterile body fluid
    - Need for respiratory support through ET tube

Study patients

- Exclusion criteria
  - Previous administration of IVIG
  - Decision by clinical staff that IVIG was either definitely needed or contraindicated

Study patients

- Infants were randomly assigned in a blinded fashion to receive either IVIG or placebo
  - Europe + Argentina: Neonatal staff opened the next sequentially numbered study pack, which was stored in the NICU
  - Australia + New Zealand: hospital pharmacy contacted and next assignment taken from a randomization list

Clinical Management

- IVIG dose was 500mg/kg, administered once and repeated after 48 hours
- Europe + Argentina: IVIG + Placebo made by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service
  - Active drug and placebo were reconstituted by clinical staff by mixing NS with freeze-dried plugs of study product, placebo was 0.2% albumin
- Australia + New Zealand: Pharmacy made up either Intragam P IVIG or placebo was (NS)

Clinical management

- Infused over 4 to 6 hours
- No further IVIG or placebo could be given after administration of the two doses
- Other aspects of management were left to the peditrician responsible for the infant's care

Primary Outcome

- Primary outcome:
  - Rate of **death** or **major disability** at age 2 years with adjustment for gestational age

Primary Outcome

- Major disability assessed with questionnaires sent to parents and health care professionals
    - Neuromotor function, Seizure, Auditory function, Communication, Visual function, Cognitive function, Other physical disability

PQ	Disability (PQ)	HSQ	Disability (HSQ)	Disability
Unable to walk even with help	Major	Has an unsteady walk	Non-major	**Major**
Has an unsteady walk but doesn't need help	Non-major	Has an unsteady walk	Non-major	**Non-major**
Walks well without help	None	Walks well without help	None	**None**
Unable to walk without help	Major	No answer	Not known	**Major**
No answer	Not known	No answer	Not known	**Not known**
Walks well without help	None			**None**
		Has an unsteady walk	None	**Non-major**

Primary Outcome

- Cognitive function assessed on basis of parental reports with the use of the validated PARCA-R (Parent Report of Children's Abilities-Revised)
  - Score of <31 on a scale 0 to 158 used to identify major cognitive delay

Secondary short-term outcomes

- Rates of death before hospital discharge
- Chronic lung disease (O2 dependency 28 days after birth)
- Major cerebral abnormality
- Relevant positive culture after trial entry (and organism)
- Pneumonia
- Necrotizing enterocolitis
- Length of hospital stay

Secondary long-term outcomes

- At 2 years with adjustment for gestational age
- Rates of death
- Rates of major disability
- Rates of nonmajor disability
  - PARCA parents' questionnaire
  - questions respiratory function, hearing, vision, hospital admissions, relevant diagnoses and current function in a number of domains, allowing categorization of disability as major or non-major

Statistical Analysis

- Original sample-size estimate based on range of rates for the primary outcome because no reliable data were available
- Intially planned: enrollment of 5000 infants
  - event rates between 15 and 30% for a power of 90% to determine a relative reduction in risk of primary outcome of 14 to 25%
- After meeting of the independent data and safety monitoring committee in 12/2005, data for 2003 infants analyzed
  - steering committee advised that the primary outcome noted to be more frequent than estimated in protocol
  - enrollment of 3500 infants would provide power of 90% to determine a relative risk reduction of 14%

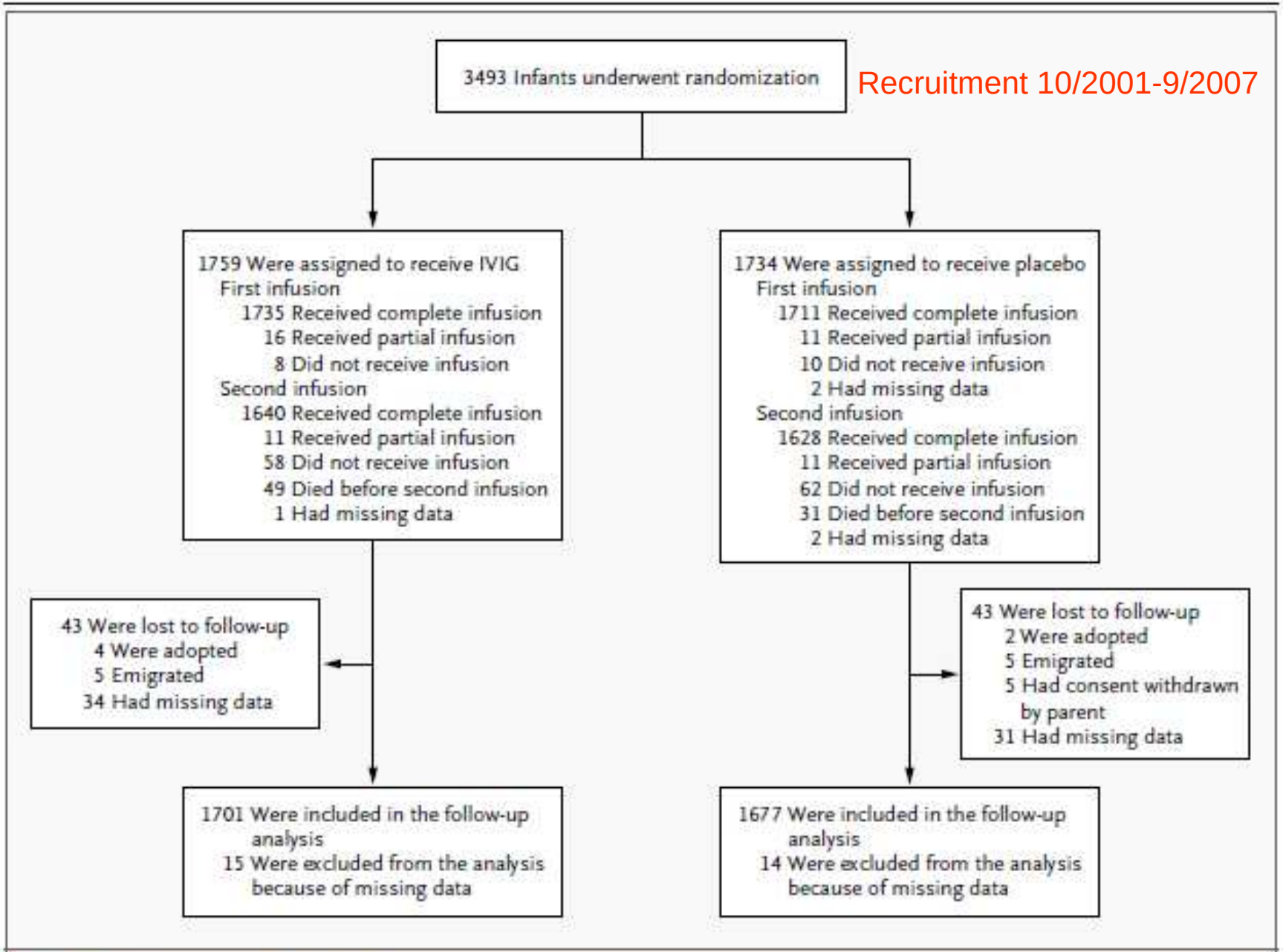


Figure 1. Enrollment and Outcomes.

IVIG denotes intravenous immune globulin.

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)

Infant and maternal characteristics were very similar in both the treatment and the placebo groups

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)

Results

- 98.3% of infants received the first infusion
- 93.5% received the second infusion
- 2.3% of infants died between the first and second infusion
- 18 infants 0.5% did not receive any infusion

Results

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)

- Of note, this result was unaltered by varying the cutoff point used to define major disability for the cognitive domain

Table 2. Main Study Outcomes.*

Outcome	Intravenous Immune Globulin	Placebo	Relative Risk (95% CI)†
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)	
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	

- Secondary Outcomes
  - No significant differences
  - Including rates of subsequent episodes of sepsis and causative organisms
  - Also no significant difference in rates of cerebral palsey (8.5% of IVIG and 8.3% of placebo)

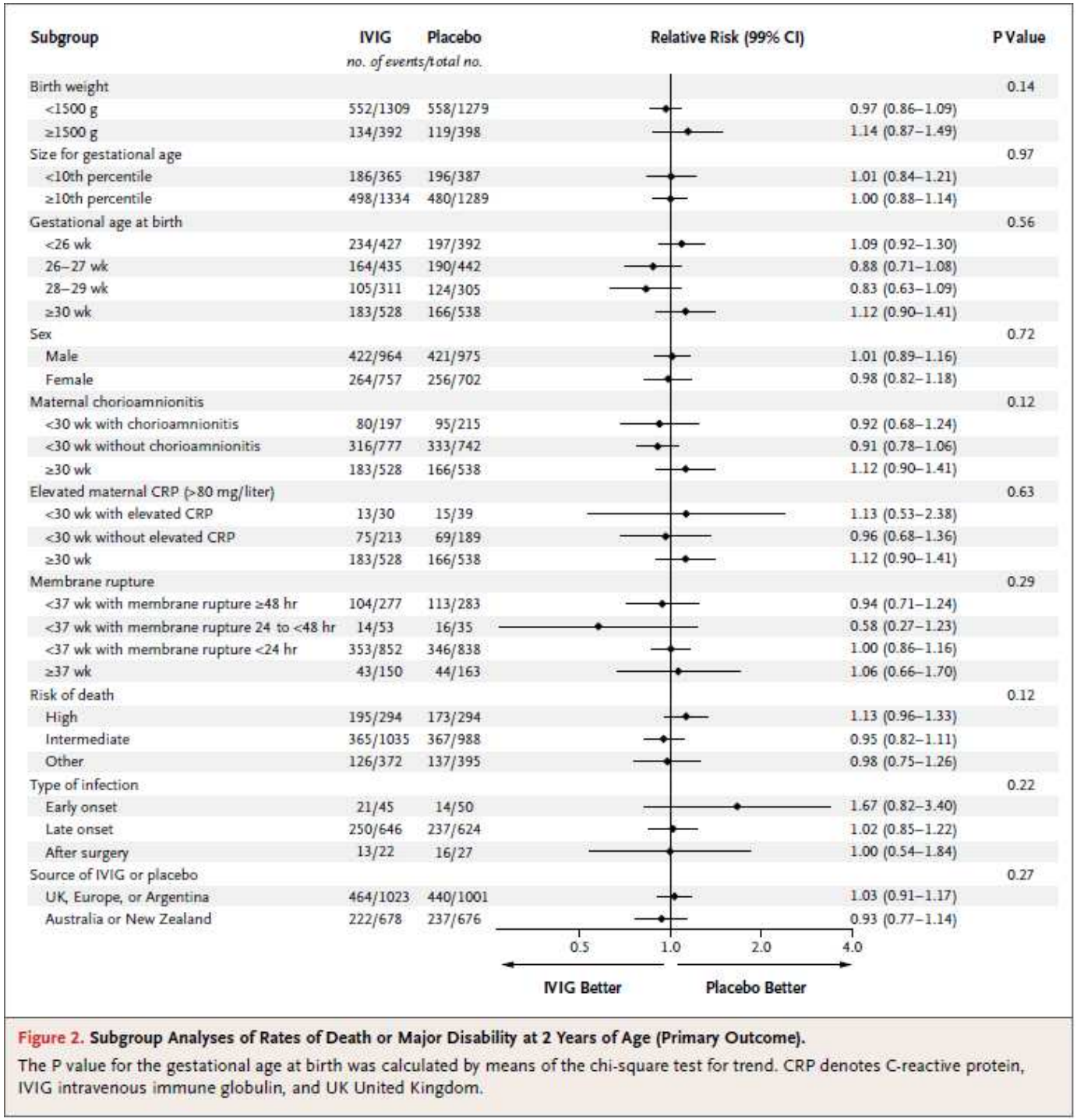


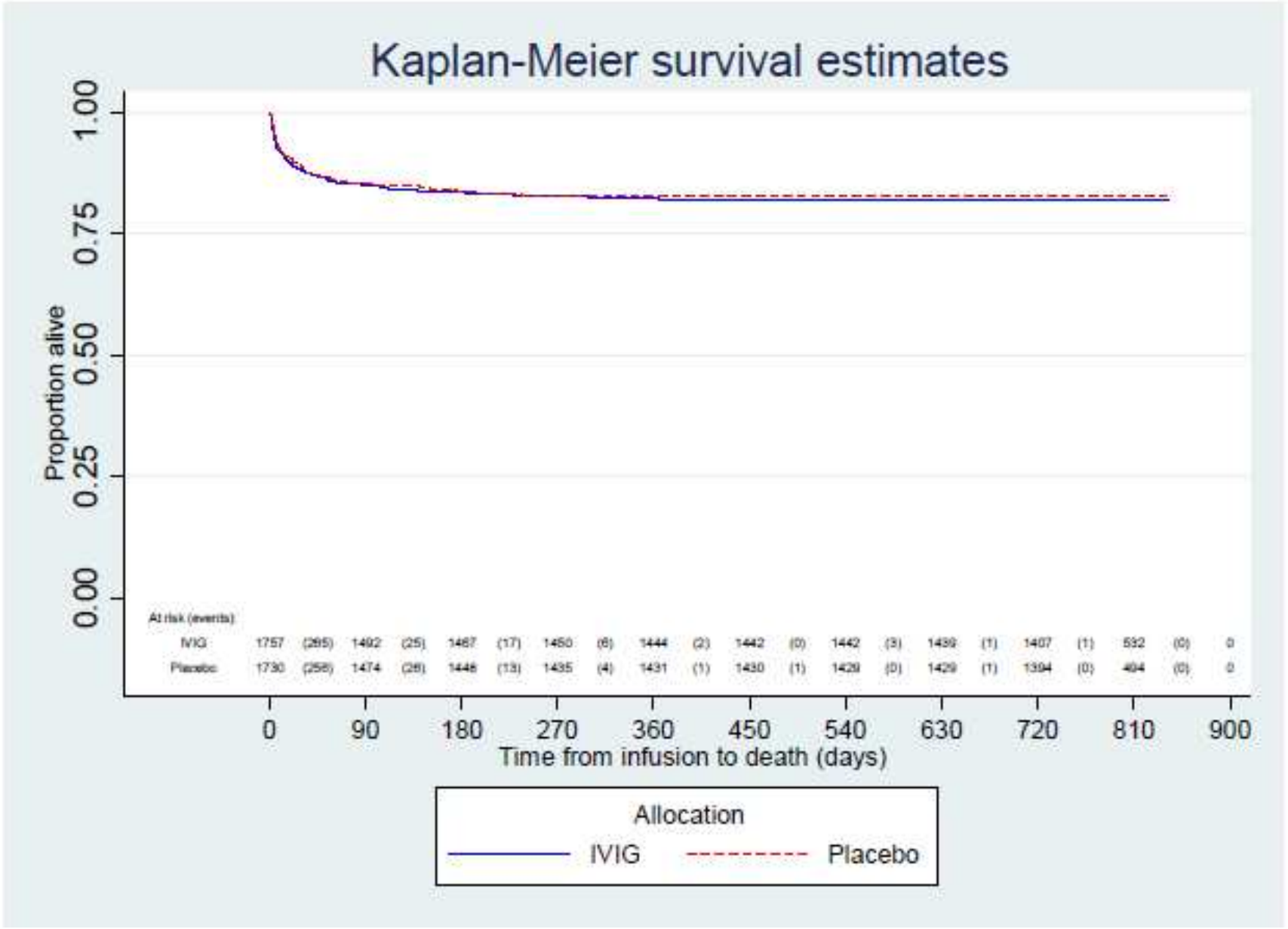
Figure 2. Subgroup Analyses of Rates of Death or Major Disability at 2 Years of Age (Primary Outcome).

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.

Subgroup Analysis of Primary Outcome:

No significant difference in any prespecified group

Figure S1: Survival curves for mortality by allocated group[2]



Discussion

- Unable to accurately determine the proportion of eligible infants who were recruited to participate in the trial
- Thresholds for study entry varied according to the center and the individual clinician
  - Serious suspected or proven infection, no micro evidence required

Discussion

- Study similar to similar to earlier trials with respect to dose of IVIG used and characteristics of infants at the time of presentation with clinical sepsis
- Compliance with the protocol was very high
- Inclusion criteria were broad
- The prespecified subgroup analysis included larger numbers of neonates than the existing meta-analyses of ALL neonatal data

Discussion

- Important feature of study is assessment of later disability
  - Information about outcome at 2 years was available for 97% of surviving infants
- On basis of established role of IVIG in modifying the course of inflammatory conditions of the CNS in adults, authors hypothesized that the immunomodulatory effects of IVIG might extend to inflammatory injury in the developing brain or lungs
  - No difference in any measure of CNS function, even when restricted to preterm infants (26 to 29 wks gestation)
  - No difference in rates of oxygen dependency at 28 days

Discussion

- In 3 earlier trials, IVIG enriched with IgM was given
  - Although these trials were small, not randomized, placebo-controlled, or blinded

Conclusion

- IVIG was not associated with significant differences in the risk of major complications or other adverse outcomes in neonates with suspected or proven sepsis