Meta-analyses of the Effectiveness of Intravenous Immune Globulin for Prevention and Treatment of Neonatal Sepsis

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ABSTRACT. *Objective.* **To determine the effectiveness of intravenous immune globulin (IVIG) in the prevention and treatment of neonatal sepsis.**

Design. **All published studies of IVIG for the prevention or treatment of neonatal sepsis were reviewed. Peer-reviewed, prospective, randomized trials with high merit were analyzed by two meta-analyses. The effect of prophylactic IVIG was evaluated by comparison of the numbers of cases of sepsis (bacteremia in the presence of systemic manifestations of sepsis), and of therapeutic IVIG by comparison of the numbers of deaths resulting from early-onset sepsis.**

Results. **Meta-analysis of 4933 evaluable newborns in 12 studies of IVIG prophylaxis showed a statistically significant negative association with the incidence of sepsis in premature low birth weight newborns given IVIG shortly after birth ($P = .0193$, two-sided). The heterogeneity across these studies precluded estimation of a common odds ratio. Meta-analysis of 110 evaluable cases of neonatal sepsis in three studies of IVIG treatment of neonatal sepsis showed a significant decrease in the mortality rate for neonates with sepsis given IVIG ($P = .007$, two-sided). The common odds ratio was .173 (95% confidence interval = .031 to .735).**

Conclusions. **Using conservative and objective outcome rating criteria, the addition of IVIG to standard therapies is of minimal but demonstrable benefit in preventing sepsis when administered prophylactically to premature low birth weight newborns, and of unequivocal benefit in preventing death when administered therapeutically for early-onset neonatal sepsis. The likelihood of newborns with sepsis living past the neonatal period was improved nearly sixfold when IVIG was administered in addition to standard therapies.** *Pediatrics* **1997;99(2). URL: http://www.pediatrics.org/cgi/content/full/99/2/e2;** ***neonatal sepsis, immune globulin.***

ABBREVIATIONS. IgG, immunoglobulin G; IVIG, intravenous immune globulin; OR, odds ratio; CI, confidence interval.

Humoral immunity of the human newborn is provided primarily by maternal immunoglobulin G (IgG) transferred transplacentally beginning at 8 to 10 weeks of gestation and accelerating during the last trimester. The lack of opsonic antibody is an important risk factor for susceptibility of newborns to infections caused by many bacteria with polysaccharide capsules (eg, group B *Streptococcus*, *Escherichia coli*, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*) that cause serious bacterial infections in newborns.[1,2] Premature infants, compared to full-term infants, have lower levels of IgG at birth that further decreases during the first few weeks of life. The relative deficiency of humoral immunity in premature newborns may contribute to the inverse correlation of birth weight and rate of neonatal sepsis, with an 86-fold increased rate of sepsis in newborns of birth weight 600 to 999 grams compared to newborns of birth weight of more than 2500 grams.[3] Infants born prematurely are also at risk for nosocomial infections resulting from prolonged hospitalization.[4]

The benefit of passive immunization by prophylactic administration of intravenous immune globulin (IVIG) for prevention of bacterial infections has been established for patients with primary agammaglobulinemia and with symptomatic human immunodeficiency virus infection.[5,6] Routine administration of IVIG for other immunocompromised hosts has not consistently been shown to clearly decrease the incidence of bacterial infections. Therapeutic IVIG and monoclonal antibodies to gram negative bacteria have been studied as adjunctive treatment for bacterial sepsis and shock but their effectiveness remains controversial.[7]

Exogenous immune globulin given at birth to premature low birth weight newborns may be beneficial for prevention of early-onset sepsis after peripartum transmission of maternal vaginal flora in the setting of low maternal antibody levels[1] and for late-onset and late, late-onset (occurring after 30 days from birth)[4] nosocomial infections.[8] The earliest studies using immune serum globulin as prophylactic immune globulin therapy in newborns failed to demonstrate effectiveness in prevention of bacterial infections probably because of the low doses of immune globulin necessitated by the intramuscular route of administration.[9–11] At least 20 English language, peer-reviewed, prospective, randomized studies from 1984 to 1994 have commented on the effectiveness of IVIG for prophylaxis of neonatal infections. These studies included populations ranging in number from 20 to 2416 newborns. The conclusions of the authors have ranged from definite or apparent reduction of infection,[12–17] to no or limited

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TABLE 1. Studies of the Efficacy of IVIG in Prevention of Neonatal Sepsis

Report and Year	Study Design	Neonates Given IVIG						Neonates Not Given IVIG			
		IVIG Formulation	Dosage Regimen	Gestational Age (Mean ± SD or Range)	Birth Weight (Mean ± SD or Range)	Neonates With Sepsis	Neonates Without Sepsis	Gestational Age (Mean ± SD or Range)	Birth Weight (Mean ± SD or Range)	Neonates With Sepsis	Neonates Without Sepsis
Haque et al, 1986	Prospective, randomized	Intraglobulin A	120 mg/kg at 2–4 h of life (one-half randomly selected received a second dose at 8 d of life)	32.4 wk (30–36)	1.14 kg (0.9–1.5)	4	96	33 wk (30–37)	1.1 kg (0.9–1.5)	5	45
Chirico et al, 1987	Prospective, randomized	Sandoglobulin	500 mg/kg on 1 d of life, and continued weekly for 1 mo (83 newborns) or while in intensive care (50 newborns)	31.3 wk (24–40)	1.51 kg (0.64–3.34)	2	66	31.7 wk (25–40)	1.63 kg (0.55–3.30)	10	55
Stabile et al, 1988	Prospective, randomized	Venogamma Polivalente	500 mg/kg on 1, 2, 3, 7, 14, 21, and 28 d of life	31 ± 2.5 wk (26–34, for both groups)	1.34 ± 0.24 kg (0.87–1.79) (both groups)	4	36	31 ± 2.5 wk (26–34) (both groups)	1.34 ± 0.24 kg (0.87–1.79) (both groups)	3	37
Clapp et al, 1989	Prospective, randomized, placebo-controlled, double-blind	Sandoglobulin	To maintain serum IgG levels at 700 mg/dl beginning at 48 h of life	30 weeks	1.3 ± 0.7 kg	0	56	31 wk	1.3 ± 0.4 kg	6	53
Bussel, 1990	Prospective, randomized, placebo-controlled, double-blind	Sandoglobulin	1 g/kg on 4 of the first 5 d of life and at 15 (−21) d of life		0.98 kg (all <1.3 kg)	9	52		1.0 kg (all <1.3 kg)	16	49
Conway et al, 1990	Prospective, randomized	Intraglobulin F	200 mg/kg within 48 h of birth and every 3 wk until hospital discharge; supplementary 100 mg/kg for suspected infection, and another 100 mg/kg for proved infection	27.5 ± 1.4 wk (all <30 wk)	1.1 ± 0.23 kg	8	21	27.5 ± 1.5 wk (all <30 wk)	1.0 ± 0.25 kg	14	12
Magny et al, 1991	Multicenter, prospective, randomized, placebo-controlled, double-blind	Biotransfusion	500 mg on 1, 2, 3, 4, 18, and 32 d of life	29.6 ± 0.2 wk (all ≤32 wk)		24	96	29.9 ± 0.2 wk (all ≤32 wk)		12	103

TABLE 1. (*Continued*)

Kinney et al, 1991	Prospective, randomized, placebo-controlled, double-blind	Gamimune N	750 mg/kg within 72 h of birth and every 14 d until hospital discharge or age 3 mo	81% appropriate for gestational age	25 < 1.0 kg; 29 1.0–1.5 kg 34 > 1.5 kg	5	83	83% appropriate for gestational age	24 < 1.0 kg; 30 1.0 – 1.5 kg 28 > 1.5 kg	5	77
Baker et al, 1992	Multicenter, prospective, randomized, placebo-controlled, double-blind	Gammagard	500 mg/kg at 3–7 d of life, 1 wk later, and every 2 wk for a total of five infusions or until hospital discharge	84% appropriate for gestational age	0.5–1.75 kg	50	237	75% appropriate for gestational age	0.5–1.75 kg	75	222
van Overmeire et al, 1993	Prospective, randomized	Sandoglobulin	500 mg within 12 h of birth, daily until 7 d of life, then weekly for 3 wk	29.6 ± 2.1 wk for both groups (all less than <32 wk)	1.15 ± 0.24 kg (0.52–1.50 kg) for both groups (all <1.5 kg)	13	43	29.2 ± 1.8 weeks for both groups (all <32 wk)	1.12 ± 0.19 kg (0.52–1.50 kg) for both groups (all <1.5 kg)	14	46
Weisman et al, 1994	Multicenter, prospective, randomized, placebo-controlled, double-blind	Sandoglobulin	500 mg/kg within 12 h of birth	29.6 ± 2.7 wk (23–25 wk)	1.25 ± 0.36 kg (0.50–1.99 kg)	40	332	29.5 ± 2.71 wk (23–34 wk)	1.25 ± 0.39 kg (0.57–2.00 kg)	39	342
Fanaroff et al, 1994	Multicenter, prospective, randomized (placebo-controlled in 51% of control infants)	Sandoglobulin	0.5–1.0 kg: 900 mg/kg; 1.0–1.5 kg: 700 mg/kg; at 1–5 d of life and every 14 d weight of 1800 g or hospital discharge	28.3 ± 2.5 wk	1.08 ± 0.25 kg	186	1018	28.4 ± 2.4 wk	1.10 ± 0.26 kg	209	1003
Totals					345	2136			408	2044	

reduction (including the two largest studies),[18–29] to a possible deleterious effect of IVIG.[30,31]

At least four prospective, randomized studies published from 1986 to 1992 have evaluated the effect of IVIG in addition to standard therapies for the treatment of neonatal sepsis.[32–35] These prospective studies included small sample sizes of 22, 31, 35, and 60 neonates with proven sepsis. Two of these studies[33,35] reported a beneficial effect with administration of IVIG. None of the four prospective studies adding IVIG to conventional treatments has individually demonstrated a statistically significant survival advantage. An additional report of the effectiveness of IVIG for treatment of sepsis suggested a beneficial effect of IVIG but used historical controls.[36]

These conflicting studies and the controversial role of exogenous IVIG in neonates for prevention and treatment of neonatal sepsis have been the subject of editorials in major medical journals that have underscored the putative and likely benefits of IVIG administration but concluded that routine use should await further definitive studies.[37–39]

Because the effectiveness of IVIG administration for prevention or treatment of neonatal sepsis remains unclear, in part due to relatively small or heterogeneous study populations, meta-analyses of these numerous small studies may be useful to: (1) assess the effectiveness of prophylactic IVIG administration in neonates to prevent sepsis; and (2) assess the effectiveness of IVIG administration as additional therapy to prevent death for neonates with proven sepsis. Meta-analysis is possible because several studies have been published in which the eligibility criteria were explicit, the schema for IVIG administration were described, definitions of proven sepsis were clear and appropriate, and the frequencies of specific outcomes (sepsis or death) were provided for treatment and control groups.

MATERIALS AND METHODS

Studies Utilized

All published studies of the effectiveness of IVIG given either prophylactically to prevent neonatal sepsis or therapeutically to treat documented neonatal sepsis were identified by personal knowledge or bibliographic search using MEDLINE. Each study was carefully scrutinized for quality of study design and rigor of scientific investigation including enrollment criteria, intervention, and description of outcomes permitting uniform application of meta-analysis criteria. Inclusion criteria for meta-analysis included: English-language (to allow our scrutiny of the study); peer-review publication; a prospective, randomized study design that included a concurrent control group receiving either a placebo or no IVIG treatment; intervention of IVIG administration either given shortly after birth for prophylaxis, or on clinical diagnosis of sepsis for treatment; ability to combine studies (including enrollment criteria, intervention, and description of outcomes); and substantial scientific merit. A meta-analysis weighted by individual study quality was not performed because of disparities resulting from use of a particular scale[40] and the recognition that, for this situation, the determination of quality can not be measured by a checklist or a unidimensional scale alone.[41]

These meta-analyses analyzed only the administration or no administration of IVIG and not the differences in dosages, administration regimens, or commercial sources. The endpoint criteria for meta-analyses were not necessarily based on the primary outcomes and conclusions reported in the original studies. To minimize bias, simple, distinct, specific, and objective endpoint criteria to determine prophylactic or therapeutic effectiveness were applied uniformly to all original studies. The effect of IVIG administered to prevent neonatal sepsis was analyzed on the basis of the outcome of a positive blood culture associated with clinical signs of systemic infection. Minor differences between studies of the definition of sepsis did not diminish the ability to identify infants fulfilling the accepted criteria for the diagnosis of sepsis.[42,43] Cases of suspected, presumed, probable, or very probable infection or sepsis were excluded. These were included in the reported results in some original studies to characterize infants with clinical signs of sepsis in the absence of a microbiologically proven infection. The effect of IVIG administered to treat early-onset neonatal sepsis was analyzed on the basis of case fatality associated with sepsis.

The original studies appropriately excluded infants with severe congenital malformation; infants with intrauterine infection, hemolytic disease, or metabolic disorders; and infants who died within 24 to 72 hours of birth (as evidence of established early onset sepsis) or who were suspected or proven to be infected at the time prophylactic IVIG administration was given. Such infants were also excluded from the meta-analyses.

Statistical Analysis

Two-by-two contingency tables were constructed to determine the relationship between IVIG administration and outcome. For determination of effectiveness, newborns were dichotomized into IVIG treated and untreated categories. For prophylactic effectiveness, outcome was dichotomized into no sepsis and sepsis groups. For therapeutic effectiveness, outcome was dichotomized into survived and died groups. Survival was narrowly defined as living past the acute episode of sepsis and did not require ultimately surviving hospitalization. Hypothesis testing was performed using asymptotic tests (χ^2) with the Robins, Breslow, and Greenland variance estimates used to calculate P values.[44] For sparse data, exact tests of proportions were used. The magnitude of association between IVIG treatment and outcome was represented by the odds ratio (OR) and 95% confidence interval (CI). A test of homogeneity across studies was performed; the criterion of $P < .10$ was used to reject the null hypothesis of homogeneity across studies. Where appropriate, summary measures across studies were estimated as a Mantel-Haenszel common OR. All statistical analyses were performed using the StatXact Turbo software (CYTEL Software Corporation, Cambridge, MA).

RESULTS

Twelve studies of the effectiveness of IVIG prophylaxis (Table 1) and three studies of the effectiveness of IVIG treatment (Table 2) fulfilled the criteria for meta-analysis. The numbers indicated in Tables 1 and 2 for each study may differ from those reported in the original studies' conclusions because meta-analysis outcome criteria required blood culture-positive sepsis. The study by Clapp et al[14] reported results for a total of 200 patients, 115 of whom were randomly assigned to IVIG and placebo groups in a double-blind fashion. The additional 85 patients were not randomly assigned due to parental refusal. These 85 patients were excluded from the meta-analysis because they were not randomized. The study by Bussel et al[15] reported episodes of sepsis in the first 30 days and for the first 70 days of life. Because IVIG was administered only as late as 15 to 21 days of life, and for comparison with other studies, the meta-analysis included only episodes of sepsis occurring during the first 30 days of life.

All studies included preterm low birth weight infants. Almost all studies had upper age or weight limits for patient entry ranging from 30 to 37 weeks (centered around 23–34 weeks), or ≤1300 to ≤ 2000 grams (centered around 1500 grams). Two studies also included a few term infants requiring intensive care, in addition to including preterm infants.[13,25]

TABLE 2. Studies of the Efficacy of IVIG in the Treatment of Neonatal Sepsis

Report and Year	Study Design	Neonates Given IVIG					Neonates Not Given IVIG			
		IVIG Formulation	Dosage Regimen	Gestational Age (Mean ± SD or Range)	Birth Weight (Mean ± SD or Range)	Lived	Died	Gestational Age (Mean ± SD or Range)	Birth Weight (Mean ± SD or Range)	Lived	Died
Sidiropoulos et al, 1986	Prospective, randomized	Sandoglobulin	Preterm: 500 mg; Term: 1000 mg; daily for 6 days	13 < 38 wk; 7 > 38 wk	11 < 2500 g; 9 > 2500 g	18	2	9 < 38 wk; 6 > 38 wk	11 < 2500 g; 9 > 2500 g	11	4
Haque et al, 1988	Prospective, randomized, placebo-controlled, double-blind	Pentaglobulin	190 mg IgG/kg/day for 4 days	33.4 wk (28–37 wk)	1.32 kg (0.85–1.6 kg)	20	1	35 wk (28–37 wk)	1.48 kg (0.9–1.7 wk)	19	4
Weisman et al, 1992	Multicenter, prospective, randomized, placebo-controlled, double-blind	Sandoglobulin	500 mg/kg once	28.2 ± 2.6 wk	1.24 ± 0.41 kg	14	0	28.5 ± 2.8 weeks	1.25 ± 0.34 kg	12	5
Totals						52	3			42	13

In each of the studies of IVIG prophylaxis the administration was begun shortly after birth, and for IVIG treatment the administration was begun when sepsis was suspected. Conventional therapies (eg, antibiotics, mechanical ventilation, cardiovascular support) were given to both IVIG-treated and -untreated groups. The exact IVIG dosages, administration regimens, and commercial sources varied between studies although all used standard preparations of pooled donor immune globulin preparations, and the timing of initial administration of IVIG was comparable (Tables 1 and 2). In eight studies of prophylactic effectiveness IVIG administration was on the day of birth; one study gave IVIG within 48 hours of birth, one within 72 hours of birth, one at 48 hours of life, and one at 3 to 7 days. Additional IVIG was administered usually at weekly (four studies), biweekly (five studies), or triweekly (one study) intervals or to maintain serum IgG levels at 700 mg/dL (1 study) until the infants reached 1 to 3 months of age or were discharged from the neonatal intensive care unit. In each study of therapeutic effectiveness of IVIG for neonatal sepsis, administration was begun as soon as diagnosis of sepsis was made clinically. In two studies IVIG was administered daily for 4 or 6 days.

Most studies reported neonates with microbiologically proven infection by positive stool or urine cultures; these cases without associated positive blood cultures were not considered diagnostic of sepsis for meta-analyses because the clinical significance requires better clinical correlation than is possible by a retrospective review. Similarly, clinical diagnoses of pneumonia and necrotizing enterocolitis without associated positive blood cultures also were not considered to be sepsis because of the diverse range of clinical presentations and inherent imprecision of definitive diagnosis in subtle cases, especially among different investigators. The difficulty of interpretation of blood cultures positive for coagulase-negative *Staphylococcus* (eg, *Staphylococcus epidermidis*) was appreciated by the investigators. Such cases were included only when bacteremia was associated with clinical signs of systemic infection. The collective effect of applying these narrow definitions excludes the detection of less-dramatic and more modest benefits of IVIG and biases the meta-analyses toward the null hypothesis; ie, no effect of IVIG on preventing development of sepsis or improving survival in infants with documented sepsis.

Several studies of the use of IVIG in neonates were not included in these meta-analyses because the studies were intended for other investigations (eg, pharmacokinetic and safety studies) that did not specifically include prospective evaluation of the effect of IVIG on infection,[18,21,34,45] because the data have appeared only in abstract form with limited information and had not been subject to peer-review,[23,28,31] or because the reports included limited information precluding critical analysis.[16,19,24] Limitations included vague or poor definition of proved sepsis (eg, positive nonquantitative cultures from catheter tips, positive bacterial antigen tests), or the inability to distinguish in the reports the numbers of blood-

culture-positive sepsis (ie, proven sepsis) from blood-culture-negative sepsis (ie, suspected or probable sepsis).

IVIG for Prevention of Neonatal Sepsis

The 12 studies represent a total of 4933 neonates including 2481 infants receiving IVIG and 2452 infants as controls. All 12 studies were prospective and randomized; 7 were placebo-controlled (usually albumin), double-blinded trials. The prophylactic effectiveness of IVIG using our outcome criteria individually and collectively for each of the 12 studies is shown in Figure 1. Five studies[12–14,17,22] demonstrated a statistically significant protective advantage for IVIG in preventing early-onset sepsis. In contrast, one study[30] showed a statistically higher sepsis rate for subjects who did receive IVIG. The remaining six studies[15,20,25–27,29] failed to show a statistically significant difference between newborns who received or did not receive IVIG treatment.

Narrow to wide ranges in 95% confidence intervals were observed that tracked with the sizes of each study population. A statistical test for homogeneity was performed to determine if there was a common measure of effect across studies. Substantial heterogeneity was observed (Breslow and Day homogeneity test χ^2 statistic = 22.49, 11 degrees of freedom, $P = .021$).[46] Therefore, a common OR cannot be estimated by pooling data across these studies. This is consistent with the visual impression of Figure 1, that the study direction for the effect of IVIG therapy was not uniform across studies. A summary statistical test was performed to test the hypothesis that prophylactic IVIG administration was associated with the risk of sepsis. Data were pooled and a stratified analysis was performed. IVIG use was significantly associated with a the rate of sepsis ($P = .0193$, two-sided). The addition of IVIG to other therapies appears to offer a slight protective advantage in the prevention of sepsis in low birth weight premature newborns. However, given the heterogeneity of these studies a positive protective advantage cannot be proven. The magnitude of protection appears to be relatively small. Including the nine episodes of sepsis in the 85 infants (10.6% incidence of sepsis) in the study by Clapp et al[14] not randomized due to parental refusal would have strengthened the finding of a beneficial effect of IVIG for the prevention of sepsis.

There are several factors that may have accounted for the great degree of heterogeneity of results observed in the meta-analysis of the 12 prophylaxis studies. One source may be subtle differences in the inclusion criteria relating to term vs preterm birth, birth weight, or a combination of criteria. Ten of the studies enrolled only premature newborns (nine studies less than 32 weeks' gestation, one study less than 34 weeks' gestation); the other two studies enrolled primarily premature but also a few full-term newborns but provided insufficient information to evaluate outcome of these two groups. The same ten studies enrolled newborns of less than 1300, 1500, 1750, or 2000 grams. One study provided sufficient information to evaluate newborns <1000 grams or ≥1000 grams; a second study provided sufficient information to evaluate newborns <1500 or ≥1500 grams. The remaining eight studies provided insufficient information to evaluate subgroups of patients. The other two studies enrolled primarily premature but also a few full-term newborns requiring neonatal intensive care but provided insufficient information to evaluate outcome of these two groups by birth weight. From these studies it is not possible to distinguish the possible differences in benefit based on term vs preterm birth, or based on birth weight divisions. There is no evidence of a gradient-response effect for studies ranked by the inclusion of extremely low-, very-low-, and low birth weight babies. However, exclusion of the two studies that included a few full-term infants did not alter the conclusions of the meta-analysis.

A subanalysis on the IVIG preparation used was

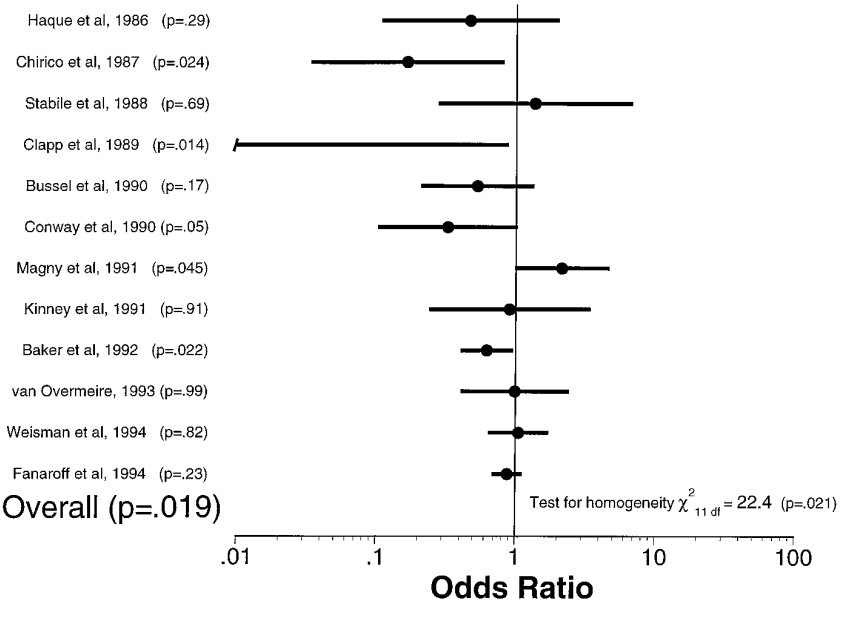

Fig 1. Separate results for the 12 studies examining the relationship between prophylactic IVIG use in neonates and the development of sepsis. Studies are listed in chronologic order. The closed circles represent the OR and the horizontal lines represent the 95% CI. The solid vertical line indicates an OR of 1.0 (no difference between neonates treated with IVIG compared to those who were not treated with IVIG). The result of the Breslow and Day homogeneity test of effect across studies is shown.[46] A two-sided test for the overall association between IVIG use and prevention of sepsis showed statistically significant association ($P = .0193$). Asymptotic methods were used for all estimates and significance tests except for the study by Clapp et al[14] for which the OR and 95% CI were calculated using exact methods.

performed on the 3659 newborns in the six studies that used a common IVIG preparation (Sandoglobulin), and on the 1274 newborns in the other six studies using six other IVIG preparations. There was evidence of significant heterogeneity of the six studies using Sandoglobulin (Breslow and Day homogeneity test χ^2 statistic = 12.25, 5 degrees of freedom, $P = .0316$) as well as the six other studies (Breslow and Day homogeneity test χ^2 statistic = 13.49, 5 degrees of freedom, $P = .0192$). Neither subgroup showed statistically significant association of IVIG with prevention of sepsis ($P = .07$ for each group).

IVIG for Treatment of Neonatal Sepsis

The three studies that addressed treatment of sepsis represent a total of 120 episodes of neonatal sepsis including 55 infants who received IVIG and the 55 infants included as controls. All three studies were prospective and randomized; two were placebo-controlled (albumin), double-blinded trials. A consistent relationship between IVIG treatment for neonates and decreased death rate was observed for all three studies (Fig 2). A test for homogeneity failed to reject the null hypothesis (Breslow and Day homogeneity test χ^2 statistic = 1.4, 2 degrees of freedom, $P = .49$)[46] permitting calculation of a common OR. There was a statistically significant relationship between IVIG administration and a decreased death rate (common OR = .173, 95% CI = .031 to .735; $P = .007$, two-sided). A common OR below 1.0 would reflect a lower mortality rate in the cohort receiving IVIG. The advantage of IVIG administration given in addition to conventional therapies is additive and increases the likelihood of survival of early-onset neonatal sepsis nearly sixfold.

DISCUSSION

The absence of type-specific opsonic antibody in the neonate has been demonstrated to predispose to bacterial infection for type Ia, Ib, and III strains of group B *Streptococcus* as a result of diminished opsonization.[1] Opsonic antibody is probably important for other neonatal pathogens as well, including coagulase-negative *Staphylococcus*.[47] The benefit of correcting this immune deficit should be most directly demonstrable in premature low birth weight newborns who do not receive a full measure of transplacental maternal antibody, and in premature or full-term newborns who clinically demonstrate this deficit as sepsis. Such benefit may not be easily detectable given the complex interactions of bacterial virulence factors (eg, attachment factors, protective factors, growth and spreading factors, toxins) and neonatal host defenses (mucosal barriers, mucosal immunity, strain type-specific antibody, complement activity, and the number and function of phagocytes) that may obscure therapeutic benefit from improvement of a single immunologic factor. Administration of IVIG probably exerts its major effect on neonatal host defenses by providing opsonic antibody against neonatal pathogens that enhance phagocytosis and killing of bacteria by neutrophils.[1,18] IVIG may also neutralize toxins, immunomodulate T cells and macrophages, especially cytokine synthesis, and affect B cell function and the complement system.[48] The beneficial effect of IVIG for treatment of sepsis is not due

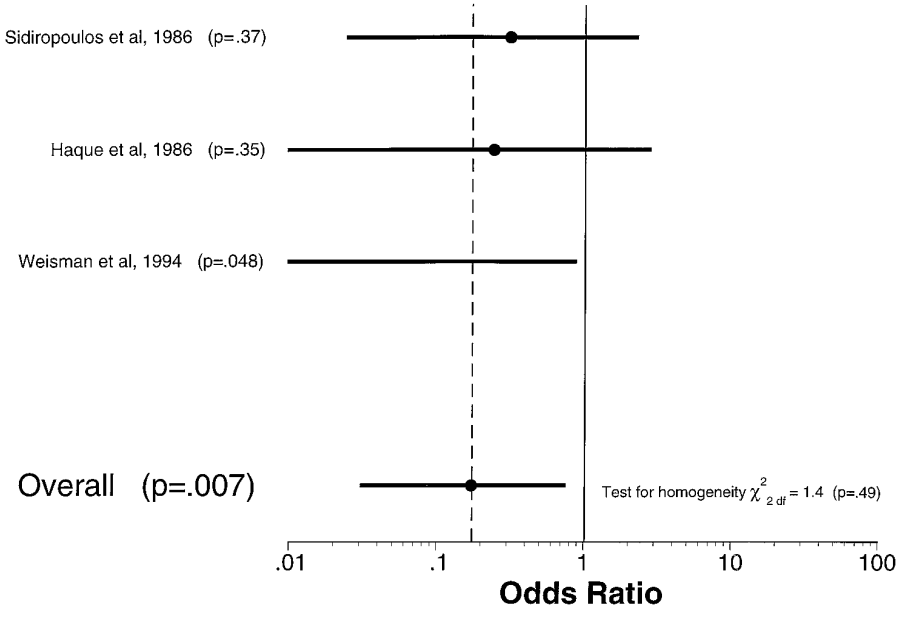

Fig 2. Separate results for the three studies examining the relationship between therapeutic IVIG use and case fatality from neonatal sepsis. Studies are listed in chronologic order. Exact methods were used for all estimates and significance tests for the assessment of treatment. The closed circles represent the OR and the horizontal lines represent the 95% CI. The solid vertical line marks an OR of 1.0 (no difference between neonates treated with IVIG compared to those who were not treated with IVIG). The result of the Breslow and Day homogeneity test of effect across studies is shown.[46] The dashed vertical line indicates the average reduction in death (common OR). The exact estimates of the common OR (closed circle) and overall 95% CI (bottom horizontal line) are shown. An exact test for homogeneity is shown at the bottom. An exact two-sided test for the overall association between IVIG treatment and decreased death rate showed statistically significant association ($P = .007$).

solely to the hemodynamic effect of colloid infusion as 75 of the 110 infants (68%) with sepsis were in the two placebo-controlled trials. The purpose of these meta-analyses was to determine any beneficial or detrimental effect regardless of the actual mechanisms that may be responsible.

The variation of the reported benefit of the effectiveness of IVIG in these studies lies in part with different and partially subjective definitions and outcomes. Many studies included all instances of infection including localized soft-tissue infections, pneumonia, urinary tract infections, gastroenteritis, and necrotizing enterocolitis even when not associated with sepsis, and included outcomes such as suspected sepsis, presumed sepsis, or very probable sepsis in addition to blood culture-proven sepsis. Unlike these broad categorizations that were defined and applied differently between studies, for this meta-analysis outcome for effectiveness for prophylactic IVIG was limited to culture-proven sepsis that required a microbiologic diagnosis (bacteremia) accompanied by clinical signs of sepsis. This outcome was a distinct, objective, unequivocal, and uniformly applicable criterion for all 12 studies. Two studies reported three infants with positive cerebrospinal fluid cultures with negative blood cultures; one infant was treated with IVIG,[20] and two infants in one study[12] were in control groups. Including these three infants in the meta-analysis had no effect on the results (test of association $P = .0101$, two-sided; significant heterogeneity precluded estimation of a common OR).

We limited analysis to the neonatal period because the prophylactic benefit of exogenous IVIG would be expected to be most demonstrable during this period. This was suggested by one study[15] reporting significantly decreased incidence of early-onset sepsis but no difference in the overall incidence of sepsis at 70 days of age. Nosocomial sepsis during the entire hospitalization reflects the contribution of numerous confounding factors and comorbidities that could not be separated. Because the majority of these low birth weight infants require aggressive therapies and instrumentation, the increased likelihood of exposure to other factors (eg, indwelling central intravenous catheters, endotracheal intubation, parenteral nutrition) may increase risk for nosocomial infections during prolonged hospitalization and would thus confound the assessment of the relationship between IVIG use and outcome. The individual and combined contribution of these risk factors is likely to be more important in the development of late-onset sepsis and especially late, late onset sepsis than is the lack of humoral immunity.[4] It is possible that IVIG administration may be of benefit throughout hospitalization but the available trials do not adequately address this issue.

The outcome criteria included bacteremia because the principal benefit of IVIG would be expected to be prevention of dissemination of extravascular infections through the bloodstream, with less effect on development of localized infections. It is possible that IVIG has additional but probably lesser benefits for localized infections. We did not evaluate the effect of prophylactic IVIG on presumed or localized infections because the differences in definitions and reporting among the studies was clinically too complex for suitable meta-analysis. Because our outcome criterion was very conservative, it was reasonable to include the six studies that were not double-blinded in design (Table 2) in the meta-analysis.

Similarly, for meta-analysis of the therapeutic effect of IVIG for neonatal sepsis it would be difficult in survivors to isolate and quantitate the graded effect of a single additional intervention such as the administration of IVIG. Death during the immediate postsepsis period was the sole outcome criterion evaluated for effectiveness of therapeutic IVIG for sepsis because it was a distinct, objective, unequivocal, and uniformly applicable criterion to all three studies. The use of death as an outcome measure is conservative in that other benefits may accrue such as decreased morbidity and decreased economic costs.

Narrow outcome criteria discount partial benefit of IVIG and biases the analysis toward the null hypothesis of no effect of IVIG administration. Because our outcomes are defined more narrowly, our analysis and interpretation of some of the results of individual studies (Tables 1 and 2) is different than that of the original authors and at variance with their published conclusions. Well-designed larger prospective studies would be necessary to determine the incremental beneficial effect of IVIG using less dramatic outcome measures.

The negative association of prophylactic IVIG with sepsis across all 12 studies ($P = .0193$), but observed inconsistently in each individual study (Breslow and Day homogeneity test $P = .021$), suggests minimal additive benefit of prophylactic IVIG when added to conventional management. Other therapies such as antimicrobial agents that are routinely offered to low birth weight premature infants are likely much more important in treating incipient infections or treating subclinical infections, and mitigate the minimal additive benefit of other therapies such as prophylactic IVIG in that setting.

The benefit of IVIG in decreasing the acute mortality associated with neonatal sepsis is demonstrable. We did not evaluate overall mortality during the entire hospitalization because the contribution of numerous confounding factors and comorbidities could not be excluded. The ultimate mortality rate of infants with neonatal sepsis reflects a multitude of complicating conditions, some of which are concomitant risk factors for sepsis and some of which are the direct sequelae of acute sepsis (although themselves noninfectious). One study[35] reported a significantly decreased acute mortality rate but no significant difference in overall survival at 56 days of life. It is likely that many infants surviving early-onset sepsis suffer comorbidities that exacerbate sequelae of sepsis or independently contribute to other high-risk conditions such as respiratory distress, intraventricular hemorrhage, pleural drainage that predispose to nosocomial infections similar to other patients without antibody deficiency. These types of infections have been referred to as late, late-onset infections

and are similar to nosocomial infections more related to factors such as instrumentation and occurring other severely ill hospitalized patients.[4] For these reasons, comparison of duration of intensive care or hospitalization or even ultimate mortality rate is not an appropriate endpoint for evaluation of IVIG for neonatal sepsis.

There was moderate variation in the dosage regimens of IVIG for both prophylaxis and treatment with the exception of timing of the initial IVIG administration for suspected sepsis. The widely recognized variability between different lots of IVIG preparations from the same manufacturer and between preparations from different manufacturers[47] has been proclaimed to indicate the need to delay further use of IVIG in newborns until issues such as determination of pathogen-specific antibodies and lot-to-lot variability can be clarified.[39] A subanalysis of the six prophylaxis studies that used the same IVIG preparation (Sandoglobulin) found a similar degree of heterogeneity as the meta-analysis of the other six studies; each subanalysis failed to show a statistically significant decrease in the incidence of sepsis. This was probably due to the minimal benefit of IVIG prophylaxis for prevention of sepsis and the fewer number of subjects in fewer studies. This subanalysis confirms that variation in IVIG preparations does not account for the heterogeneity of the IVIG prophylaxis studies. Because eight different IVIG preparations and different specific dosage regimens were used in these studies there is no bias for the use of a particular IVIG preparation or dosage regimen. This meta-analysis may be more reflective of the wide variation in practice for the administration of IVIG than a study using a single IVIG preparation from one manufacturer. This speaks to the meta-analysis being useful to summarize effectiveness rather than the efficacy. The overall effectiveness despite this diversity indicates precisely that, for these purposes, recommendation of a specific commercial IVIG preparation or dosage regimen is not as important as simply whether or not IVIG is administered. It is intuitive that prophylactic administration of IVIG for low birth weight premature newborns should be shortly after birth, and the consensus of these studies indicates that it is well tolerated and, if used, should be administered within the first 12 to 24 hours of life. Administration of IVIG for sepsis should follow shortly after the diagnosis or suspicion of sepsis.

From the published reports it was not possible to evaluate the effect of IVIG on prophylactic effectiveness for specific bacterial species. The largest study[27] did not list the causative organisms and some studies[15,17,30] did not list organisms causing systemic infection as opposed to localized infection, thus precluding further evaluation. The data for one study[13] were subsequently published in response to a letter to the editor.[49]

These meta-analyses differ substantially from those performed by Lacy and Ohlsson[50] by having stricter outcome criteria for effectiveness (incidence of microbiologic and clinical sepsis for IVIG prophylaxis; or death for IVIG therapy) applied uniformly across all studies, and excluding several studies included in their analyses. Our meta-analyses excluded reports appearing only in abstract form with limited information that had not undergone peer-review,[23,28,31] short-term metabolic studies that were not designed to study the effect of IVIG on infection,[21] and reports that contained significant methodologic flaws or that reported limited data that precluded critical analysis.[16,19] Our meta-analyses included an additional study of IVIG for prophylaxis[25] and an additional study of IVIG for treatment.[32] Only four additional IVIG prophylaxis studies[16,21,23,28] provided sufficient information to even consider extrapolation and analysis using our outcome criteria of microbiologic and clinical documentation of sepsis. Including these four studies (which violated our experimental design) in the meta-analysis had no effect on the results (Breslow and Day homogeneity test χ^2 statistic = 25.85, 14 degrees of freedom [one study was uninformative], $P = .027$, the heterogeneity precluded estimation of a common OR; association of IVIG use with a decreased rate of sepsis $P = .027$, two-sided).[46]

Neither meta-analysis included two additional reports of IVIG for treatment of sepsis.[34,36] The report by Friedman et al[36] was not included in our meta-analysis because the study was not of a randomized study design. Neonates with sepsis were compared retrospectively using a case-control design to historical controls matched for neutropenia and high levels of group B *Streptococcus* antigen at the time of diagnosis. The report by Christensen et al[34] was not included because the diagnosis of sepsis did not require a positive blood culture and included cases diagnosed only by a positive tracheal culture or bacterial antigen test, each of which could result in an overdiagnosis of sepsis. The number of neonates with culture-positive sepsis could not be ascertained from that report. However, no deaths occurred in either the IVIG-treated group or the control group making this study statistically uninformative. If the results from these two studies (two deaths in 23 neonates given IVIG and seven deaths in 23 neonates not given IVIG) were included in the meta-analysis, the differences are more apparent (OR = .163 and 95% CI = .054 to .495).

Determination of the effectiveness of IVIG in the prevention and treatment of neonatal sepsis emphasizes the usefulness of meta-analysis to discern differences between study groups that are not apparent with smaller individual studies. A statistically significant association ($P = .0193$) was found by meta-analysis between the incidence of sepsis and use of IVIG in newborns for prophylaxis. This demonstrated the increase in statistical power by the pooling of data across studies, although the magnitude of the difference in this meta-analysis could not be estimated because of the heterogeneity among the reported studies (Fig 1). This heterogeneity probably belies the minimal benefit, at most, of prophylactic IVIG in this setting. Even for the largest single study of 2416 newborns,[27] also having the narrowest confidence interval (CI = .71 to 1.09) among the 12 studies, only a 1.79% decrease in incident sepsis was detected that was not statistically significant

($P = .23$). Detection of a difference this small would have required accrual of 10 548 subjects in each study group to have 80% power to detect such a small difference ($\alpha = .05$, one-sided). For comparison, detection of a 5% difference would have required 1237 subjects in each group. A statistically significant difference ($P = .0193$) was found in the meta-analysis of all studies with a combined total of 4933 newborns, suggesting an increase in statistical power derived by the pooling of data across studies. Thus, it is not surprising that the benefit of IVIG for prophylaxis was not statistically significant even in the largest single study of 2416 neonates.[27]

The three studies of the effectiveness of IVIG in the treatment of neonatal sepsis each showed a benefit but was not statistically significant (Fig 2). Meta-analysis of these studies improved the power to detect a true difference and, in fact, demonstrated a statistically significant ($P = .007$) decrease in the case fatality rate in the IVIG-treated group. This, along with the apparent lack of homogeneity (Breslow and Day homogeneity test $P = .49$) across studies supports the notion that there is a true benefit derived from treating sepsis with IVIG that is not clearly apparent in the individual studies due to small study groups (31, 35, and 44 total patients).

The role of IVIG as prophylaxis for low birth weight premature infants will likely remain controversial. This analysis is not inconsistent with the hypothesis that exogenous antibody administered as IVIG provides incremental additive benefit to conventional management in the prevention of neonatal sepsis in low birth weight premature newborns. Efforts to develop antibody formulations specifically designed to enhance this mode of therapy are appropriate. Appropriate cost-effectiveness analyses would be necessary to justify the routine prophylactic administration of IVIG administration for this relatively large population given the minimal benefit demonstrated thus far.

Conversely, the additive benefit of IVIG given to neonates with sepsis in decreasing acute mortality is clearly unequivocal and substantial. Neonates with sepsis not afforded this therapy suffer a nearly sixfold higher short-term mortality rate. Meta-analysis of these studies supports administration of a single dose of 500 to 750 mg/kg IVIG to neonates with sepsis. It is not clear from these analyses if there is any additional benefit from additional doses. The additional financial cost for this much smaller population of patients would not be prohibitive as part of the routine therapy for neonatal sepsis. Use of IVIG preparations incorporating solvent-detergent treatment is desirable to minimize transmission of viruses and should not affect the conclusions of these meta-analyses despite the use of other IVIG preparations in the original studies.

Because of the limitations of the studies examined, these analyses have not addressed the role of IVIG for cases of localized neonatal infections or for suspected sepsis without bacteremia. Furthermore, the peculiar aspects of neonatal bacterial infections also do not warrant extrapolation of these conclusions to other populations or clinical circumstances.

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