

Meta-analysis: Intravenous Immunoglobulin in Critically Ill Adult Patients with Sepsis

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Background: Intravenous immunoglobulin therapy has been proposed as an adjuvant treatment for sepsis. Yet, its benefit remains unclear, and its use is not currently recommended.

Purpose: To evaluate the effect of polyclonal intravenous immunoglobulin therapy on death in critically ill adult patients with sepsis.

Data Sources: MEDLINE (1966 to May 2006) and the Cochrane Central Register of Controlled Trials (May 2006 edition).

Study Selection: All randomized, controlled trials of critically ill adult patients with sepsis, severe sepsis, or septic shock who received polyclonal intravenous immunoglobulin therapy or placebo or no intervention were selected. No restrictions were made for study language or type of publication.

Data extraction: Data were independently extracted by 2 investigators using a standardized form.

Data Synthesis: The literature search identified 4096 articles, of which 33 were deemed to be potentially eligible. Twenty trials ($n = 2621$) met eligibility criteria and were included in the analysis. Polyclonal intravenous immunoglobulin therapy was associated with an overall survival benefit (risk ratio, 0.74 [95% CI, 0.62 to 0.89]) compared with placebo or no intervention. In sensitivity analyses, documented survival improved when the analysis was limited to

published, peer-reviewed trials (risk ratio, 0.72 [CI, 0.58 to 0.89]) (17 trials [$n = 1865$]) and blinded trials (risk ratio, 0.61 [CI, 0.40 to 0.93]) (7 trials [$n = 896$]). Severe sepsis or septic shock (risk ratio, 0.64 [CI, 0.52 to 0.79]) (11 trials [$n = 689$]), receiving a total dose regimen of 1 gram or more per kilogram of body weight (risk ratio, 0.61 [CI, 0.40 to 0.94]) (7 trials [$n = 560$]), and receiving therapy for longer than 2 days (risk ratio, 0.66 [CI, 0.53 to 0.82]) (17 trials [$n = 1847$]) were strongly associated with this survival benefit.

Limitations: Most trials were published before new developments modifying the care and outcome of critically ill patients with sepsis including early goal-directed therapy and activated protein C treatment, were introduced.

Conclusions: A survival benefit was observed for patients with sepsis who received polyclonal intravenous immunoglobulin therapy compared with those who received placebo or no intervention. A large, randomized, controlled trial of polyclonal intravenous immunoglobulin therapy should be performed on the basis of the methodological limitations of the current literature, the potential benefit from this therapy in more severely ill patients, and the potential effect of dosage and duration of this therapy.

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Severe infections are a leading cause of death in the intensive care unit (ICU), with a mortality rate ranging from 20% for sepsis to 50% for septic shock (1, 2). During the past 25 years, researchers have focused on controlling the overwhelming inflammatory response after bacterial invasion. Before the publication of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which evaluated activated protein C (3), few immune or coagulation modulators that improved survival had been found. Physicians use intravenous immunoglobulin (IVIG), a fractionated blood product, for treating a variety of health conditions. On the basis of the concept of modulation of the inflammatory cascade during sepsis, IVIG may be a useful adjuvant treatment. Its exact mechanism of action when used to treat sepsis remains unknown, but it exceeds a direct antigen–antibody reaction (4). Recent consensus guidelines do not recommend the widespread use of IVIG in patients with severe sepsis or septic shock (5, 6). Instead, IVIG use is suggested as a therapy in group A streptococcal toxic shock syndrome (7). Despite these recommendations, 15% of the off-label use of IVIG in the United States is to treat a broad range of infectious diseases (8).

Two meta-analyses that evaluated the effect of polyclonal IVIG on death in patients with sepsis produced con-

flicting results. In a systematic review (9) published in the Cochrane Library and favoring IVIG, researchers pooled results from 6 studies of adults. A large, unpublished trial was not considered to be eligible for that review (10). Conversely, in a recent meta-analysis not favoring IVIG, researchers pooled results from many studies and included adult and neonatal populations, which differ in acquired humoral immunity (11). Thus, some concerns preclude definitive conclusion of their results on the effect of polyclonal IVIG in the adult population. We performed this systematic review to determine the survival benefit of polyclonal IVIG in critically ill adult patients with sepsis, severe sepsis, or septic shock.

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Context

Effects of polyclonal intravenous immunoglobulin therapy (IVIG) on the mortality rate of critically ill patients with sepsis are unclear.

Contribution

This meta-analysis of 20 randomized trials that studied 2621 critically ill adult patients with sepsis found that treatment with polyclonal IVIG decreased the risk for death more than placebo or no intervention (risk ratio, 0.74 [95% CI, 0.62 to 0.89]). Survival benefits seemed most prominent with higher doses and prolonged administration of IVIG and in more severely ill patients.

Cautions

Because most trials had methodological limitations and were performed before modern intensive care management strategies, the authors recommend that a large trial be performed to confirm the findings.

—The Editors

METHODS

Search Strategy

We developed a systematic search strategy that we applied to MEDLINE (1966 to May 2006) and the Cochrane Central Register of Controlled Trials (May 2006 edition) to identify randomized, controlled trials that evaluated IVIG as a mode of therapy, regardless of the clinical field associated with studies. The strategy combined the text terms *ivig*, *igiv*, *intravenous immune globulin*, *intravenous immunoglobulin*, *gammagard*, *vigam*, *gamimmune*, *flebo-gamma*, *sandoglobulin*, *iveegam*, *pentaglobin*, *intraglobin*, *endoglobulin*, and *gammaglobulin* by using the Dickersin filter for randomized, controlled trials (12). The bibliographies of all identified meta-analyses and trials were also reviewed to identify relevant reports. Two authors independently reviewed citations retrieved from the electronic search to identify potentially relevant trials for this review. When a unanimous decision could not be reached, a third party was consulted.

Study Selection

To be eligible, studies had to be randomized, controlled trials comparing IVIG therapy with placebo or no intervention in critically ill adult patients with sepsis. We considered trials to be conducted in adults if most patients were 18 years of age or older. Sepsis was defined according to the American College of Chest Physicians (ACCP)–Society of Critical Care Medicine (SCCM) guidelines (13) or was extrapolated to these criteria if not provided. The primary outcome measure was death, and the secondary outcomes were length of stay in the ICU and days of mechanical ventilation. We did not restrict study eligibility to language or type of publication.

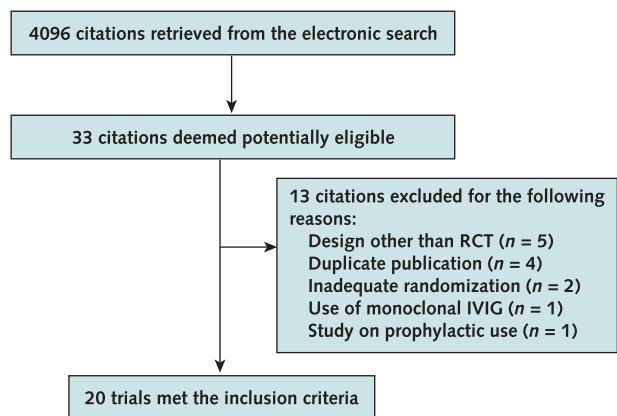
Data Abstraction

We developed a standardized data abstraction form that included the country of study origin, methods of therapy compared, dosage and duration of treatment, the number of patients randomly assigned to each treatment group, length of follow-up, patient demographic characteristics, all pertinent outcome information, and adverse events and withdrawals within each treatment group. We consulted a translator for each relevant reference that was published in a foreign language. If data abstractors were unclear on any information of interest in an included study, we contacted study authors for them to clarify the methods or provide additional data as needed.

Data Synthesis

We used random-effects models to synthesize data from included studies according to the DerSimonian–Laird method, as suggested when between-study heterogeneity is suspected (14). For circumstances in which pooling of trials was inappropriate, we provide a qualitative discussion of the findings. We analyzed discrete and continuous data by using Review Manager, version 4.2.7 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). We expressed dichotomous data measures of effect, such as death, as risk ratios with 95% CIs. A risk ratio less than 1.0 suggested a reduced risk for death for patients in the IVIG group compared with those in the control group. A risk ratio greater than 1.0 suggested an increased risk for death for patients in the IVIG group compared with those in the control group. For continuous data, we expressed measures of effect, such as length of stay in the ICU or days of mechanical ventilation, as weighted mean differences with 95% CIs. We performed statistical tests for heterogeneity (a *P* value < 0.10 indicated statistical significance) and investigated *I*² measures of consistency across trials (15). We tried to discover and explain the primary sources of the

Figure 1. Study flow diagram.



IVIG = intravenous immunoglobulin.

Table 1. Baseline Characteristics of Patients, Minimal Inclusion Criteria, and Intravenous Immunoglobulin Regimen*

Author, Year (Reference)	Patients, n	Mean Age (SD), y		Inclusion Criteria	Reported Severity of Illness Measures		Treatment Regimens	Total Dose, g/kg of body weight	Duration of Therapy, d
		IVIG Group	Control Group		IVIG Group	Control Group			
Lindquist et al., 1981 (17)	67	48.3	39.2	Sepsis secondary to septicemia (Svanbom criteria) (reference 37)	NR	NR	Gamma-Venin (ZLB Behring, King of Prussia, Pennsylvania) (days 0–2, 0.15 g/kg; then every wk as needed) vs. no intervention	0.45	3 (+ as needed)
Just et al., 1986 (18)	104	40.2 (18.5)	40.2 (18.6)	Sepsis mainly after surgery or trauma (Center for Disease Control criteria) (reference 38)	NR	NR	Firma (Biotest Pharma, Frankfurt, Germany) (5 g every 12 h for 4 doses) vs. no intervention	0.30†	2
Jesdinsky et al., 1987 (19)	288	53.8 (17.5)	55.1 (19.0)	Sepsis from abdominal infections	NR	NR	Immunoglobulin 7S (Armour Pharma, Eschwege, Germany) (day 0, 10/g; days 1 to 4, 20.5 g) vs. no intervention	1.35†	5
Spannbrucker, 1987 (20), and Vogel et al., 1988 (21)	50	50.8 (15.5)	54.5 (12.0)	Septic shock	NR	NR	Pentaglobin (Biotest Pharma, Germany) (days 0 to 2, 0.15 g/kg) vs. no intervention	0.45	3
De Simone et al., 1988 (22)	24	45 (4)	34 (5)	Severe sepsis	NR	NR	Sandoglobulin (Sandoz Pharmaceutical, Milan, Italy) (day 1, 0.4 g/kg; day 2, 0.2 g/kg; day 7, 0.4 g/kg [as needed]) vs. no intervention	0.60	2 (+ as needed)
Grundmann and Hornung, 1988 (23)	46	46.9	52.8	Sepsis from gram-negative bacteriemia with positive endotoxin (sepsis score ≥12)	Mean sepsis score 17.0 (SD, 4.0)	Mean sepsis score 18.9 (SD, 4.8)	Intraglobin F (Biotest Pharma, Frankfurt, Germany) days 0 and 1, 0.25 g/kg, vs. no intervention	0.50	2
Wesoly et al., 1990 (24)	35	44.7 (19)	54.8 (17)	Sepsis after surgery (sepsis score ≥12)	Mean sepsis score 14.8 (SD, 2.5)	Mean sepsis score 16.3 (SD, 3.6)	Pentaglobin (Biotest Pharma, Germany) (days 0–2, 0.25 g/kg) vs. no intervention	0.75	3
Burns et al., 1991 (25)	38	61.5	59.8	Sepsis and thrombocytopenia	NR	NR	Sandoglobulin (Sandoz Pharmaceutical, Milan, Italy) (days 0–2, 0.4 g/kg) vs. albumin	1.2	3
Dominioni et al., 1991 (26)‡	62	67 (10)	68 (12)	Severe sepsis after surgery or trauma (sepsis score ≥20)	Mean sepsis score, 24 (SD, 4); mean APACHE II score, 17 (SD, 5)	Mean sepsis score, 24 (SD, 3); mean APACHE II score, 18 (SD, 5)	Sandoglobulin (Sandoz Pharmaceutical, Basel, Switzerland) (days 0 and 1, 0.4 g/kg, day 5; 0.2 g/kg) vs. human albumin in 5% dextrose in water	1	2 + 1§

Continued on following page

Table 1—Continued

Author, Year (Reference)	Patients, n	Mean Age (SD), y		Inclusion Criteria	Reported Severity of Illness Measures		Treatment Regimens	Total Dose, g/kg of body weight	Duration of Therapy, d
		IVIIG Group	Control Group		IVIIG Group	Control Group			
Schedel et al., 1991 (27)‡	69	46 (16)	37 (18)	Severe sepsis	APACHE II score, 30; unsure whether mean or median	APACHE II score, 24; unsure whether mean or median	Pentaglobin (Biotest Pharma, Dreieich, Germany) (day 0, 30 g; days 1 and 2, 15 g) vs. no intervention	0.85†	3
Behre et al., 1995 (28)‡	52	50	55§	Severe sepsis with hematologic malignant condition and neutropenia (ACCP/SCCM criteria) (reference 13)	NR	NR	Pentaglobin (Biotest Pharma Dreieich, Germany) (time 0, 10 g; then 5 g every 6 h for 72 h) vs. 5% human albumin	0.9†	3
Dominioni et al., 1996 (29)‡¶	55	55 (19)	57 (19)	Severe sepsis after surgery or trauma (sepsis score ≥16)	Mean sepsis score, 23 (SD, 4)	Mean sepsis score, 23 (SD, 4)	Sandoglobulin (Sandoz Pharmaceutical, Basel, Switzerland) (days 0 and 1, 0.4 g/kg; day 5, 0.2 g/kg) vs. human albumin in 5% dextrose in water and saline solution	1	2 + 1§
Werdan et al., 1997 (10)‡	652	NR	NR	APACHE II score of 20–35; sepsis, severe sepsis, or septic shock (sepsis score ≥12)	NR; inclusion criteria indicate a range of APACHE II scores of 20–35¶**	NR; inclusion criteria indicate a range of APACHE II scores of 20–35¶**	Polyglobin N (Bayer, Germany) (day 0, 0.6 g/kg; day 1, 0.3 g/kg) vs. 0.1% albumin in 10% maltose	0.9**	2**
Yakut et al., 1998 (30)	40	32 (16)	31 (16)	Severe sepsis postsurgery (sepsis score ≥16)	Mean sepsis score, 20 (SD, 4); mean APACHE II score, 16 (SD, 4)	Mean sepsis score, 20 (SD, 3); mean APACHE II score, 16 (SD, 5)	Gamumin N (Miles Inc., Pharmaceutical Division, Elkhart, Indiana) (days 0 and 1, 0.4 g/kg; days 2–4, 0.2 g/kg) vs. human albumin	1.4	5
Masaoka et al., 2000 (31)‡	682	<65 ††	<65 ††	Sepsis mainly with neutropenia after chemotherapy	NR	NR	IVIIG nonspecified (days 3–5, 5 g) vs. no intervention	0.2†	3
Tugrul et al., 2002 (32)	42	42.0 (18)	49.3 (20.6)	Severe sepsis (ACCP/SCCM criteria) (reference 13)	Mean APACHE II score, 10.5 (SD, 4.6); mean SOFA score 5.0 (SD, 2.7); mean GCS score, 14.2 (SD, 2.1)	Mean APACHE II score, 14.0 (SD, 8.5); mean SOFA score, 5.7 (SD, 4.0); mean GCS score 12.9 (SD, 4.0)	Pentaglobin (Biotest Pharma, Dreieich, Germany) (days 0–2, 0.25 g/kg) vs. standard sepsis therapy	0.75	3
Karatzas et al., 2002 (33)	82	50.5 (3.3)	50.7 (7.4)	Severe sepsis (ACCP/SCCM criteria) (reference 13)	Mean APACHE II score, 21.3 (SD, 7.2)	Mean APACHE II score, 23.5 (SD, 7.9)	Pentaglobin (Biotest Pharma, Dreieich, Germany) (days 0–2, 0.25 g/kg) vs. standard sepsis therapy	0.75	3

Table 1—Continued

Author, Year (Reference)	Patients, n	Mean Age (SD), y		Inclusion Criteria	Reported Severity of Illness Measures		Treatment Regimens	Total Dose, g/kg of body weight	Duration of Therapy, d
		IVIG Group	Control Group		IVIG Group	Control Group			
Darenberg et al., 2003 (34)†	21	53 (NR)	51 (NR)	Septic shock from group A streptococci (ACCP/SCCM criteria) (reference 13)	SAPS II score, 53; SOFA score, 11	SAPS II score, 51; SOFA score, 11	Endoglobulin (Baxter) (day 0, 1 g/kg; days 1 and 2, 0.5 g/kg) vs. 1% albumin	2	3
Rodríguez et al., 2005 (35)‡	56	61.3 (19.9)	65.9 (18.2)	Sepsis from abdominal infections (ACCP/SCCM criteria) (reference 13)	Mean APACHE II score, 16.1 (SD, 5.9); mean TISS score, 19.0 (SD, 6.5) (day 1)	Mean APACHE II score, 15.2 (SD, 6.1); mean TISS score, 21.3 (SD, 9.3) (day 1)	Pentaglobin (Biotest Pharma, Frankfurt, Germany) (days 0–4, 0.35 g/kg) vs. 5% human albumin	1.75	5
Henrich et al., 2006 (36)†	206	48.8	51.0	Severe sepsis or septic shock (ACCP/SCCM criteria) (reference 13) with hematologic malignant condition and neutropenia	NR	NR	Pentaglobin (Biotest Pharma, Dreieich, Germany) (time 0, 10 g; then 5 g every 6 h for 72 h) vs. 5% human albumin	0.9†	3

* All sepsis scores refer to reference 39. ACCP/SCCM = American College of Chest Physicians/Society of Critical Care Medicine; APACHE II = Acute Physiology and Chronic Health Evaluation II; GCS = Glasgow Coma Scale; IVIG = intravenous immunoglobulin; NR = not reported; SAPS II = Simplified Acute Physiologic Score II; SOFA = Sepsis-related Organ Failure Assessment; TISS = Therapeutic Intervention Scoring System.
 † Based on a patient who weighs 70 kg.
 ‡ Multicenter trial.
 § Median age.
 || The added number represents an additional day of therapy after the first uninterrupted course.
 ¶ Patients from a previous study (n = 62) (26) were removed from the total sample size (n = 117). Raw data for age could not be extracted; mean age is representative of all 117 patients and includes patients from the previous study.
 ** Based on a protocol published before the study was performed (40).
 †† Data are presented as age categories (80% of patients were in each age category).

heterogeneity. We hypothesized that methodological differences, differences in diagnosis and severity of disease, differences in the treatment regimen, or simply chance would explain heterogeneity. Thus, we performed a series of sensitivity analyses based on study characteristics (high methodological quality, published and peer-reviewed trials, double-blind studies, diagnosis and severity, dose regimen, duration of therapy, timing of administration, and period of publication) to further explore heterogeneity and evaluate the robustness of our findings. For independent subgroups of trials, we assessed interaction by using a mixed-effects model.

We used the Jadad scale to assess some variables of trial methods (16). This scale provides scoring for randomization (0 to 2 points), double-blinding (0 to 2 points), and withdrawals (1 point), with scores ranging from 0 to 5. We used available peer-reviewed, published information and information from authors to assess studies for methodological quality studies. However, we considered only peer-reviewed, published trials that obtained a Jadad score of 5 to be of high methodological quality.

Role of the Funding Source

The Ontario Ministry of Health and Long-Term Care, Ontario, Canada, provided funding for the study. The funding source had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication. Dr. Turgeon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

Search Results

We identified 4096 citations of randomized, controlled trials of IVIG (3300 from MEDLINE and 796 from the Cochrane Central Register of Controlled Trials) (Figure 1) by using the systematic literature search. We deemed 33 citations to be potentially eligible. We excluded 13 studies for the following reasons: design other than a randomized, controlled trial (n = 5); duplicate publication (n = 4); inadequate randomization procedure (n = 2); use of monoclonal IVIG (n = 1); and study on prophylactic

use of IVIG ($n = 1$). Twenty trials of 2621 patients met inclusion criteria for our review (Figure 1 and Table 1).

Study Characteristics

Among the selected trials, 15 were published in English (10, 17, 19, 22, 23, 25–29, 32–36), 3 in German (18, 20, 24), 1 in Turkish (30), and 1 in Japanese (31). Eighteen trials were conducted in Europe (10, 17–19, 21–24, 26–30, 32–36), 1 in North America (25), and 1 in Asia (31). Seventeen of the selected trials were published as articles (17, 18, 21–32, 34–36), 1 as an abstract (10), 1 as an abstract and a book chapter (20, 21), and 1 as a letter (33) (Table 2). All trials published as articles were peer-reviewed but only 7 were blinded (10, 25, 26, 29, 30, 34, 35) (Table 2). Nine studies were multicenter studies (10, 21, 26, 28, 29, 31, 34–36), including 2 large trials (10, 31). Two trials enrolled a total of 4 patients younger than 18 years of age (23, 32); in 3 other trials, the age restriction was 15 years of age or older (26, 29) and 14 years of age or older (19). In 1 trial (19), 17% of included patients did not meet inclusion criteria, and in another trial (31), 20% of patients had severe infections instead of sepsis. One trial (29) included data from a previous trial (26) that we removed and analyzed separately because of different inclusion criteria.

In our review, the 20 trials that we included were designed to administer polyclonal IVIG, a placebo regimen, or no intervention on the first day (day 0) after the diagnosis of sepsis, with the exception of 2 trials: 1 in which patients received the regimen on day 1 after diagnosis (22) and 1 in which patients received the regimen on day 3 after diagnosis (31). All trials reported data on death at different lengths of follow-up (Table 2). Eight trials reported data on length of stay in the ICU (18, 23, 24, 26, 29, 30, 32, 35), and 2 studies reported data on duration of mechanical ventilation (23, 24). Six trials reported adverse effects in the IVIG group ranging from mild (vomiting and chills) to severe (dyspnea, allergic reaction, and shock) (17, 19, 23, 31, 34, 36). We contacted the authors of 5 trials to obtain additional data or clarification on the methods (10, 25, 31–33). We also used outcome data from a previous peer-reviewed meta-analysis (11) that researchers used in 2 trials (10, 33).

Assessment of Validity

Three studies were considered to be of high methodological quality (25, 34, 35) (Table 2). Five studies reported losses to follow-up that ranged from 3% to 20% of patients (10, 17, 27, 31, 36) (Table 2). Statistical analysis was performed according to an intention-to-treat principle in 16 trials but was poorly reported in the remaining 4 trials (17, 18, 27, 28) (Table 2). The minimal inclusion criterion was sepsis. Study researchers used ACCP/SCCM criteria (13) in 6 trials to define the severity of sepsis (28, 32–36) and used the sepsis score (39) in 6 trials (10, 23, 24, 26, 29, 30). The remaining trials used a different scoring system or had their own criteria (17–20, 22, 25, 27,

31). Sepsis was either suspected or proven in all patients (Table 1). Nine trials used sepsis as the minimal inclusion criterion (10, 17–19, 23–25, 31, 35), and the remaining 11 trials (20, 22, 26–30, 32–34, 36) used severe sepsis or septic shock as the minimal inclusion criterion. Six trials enrolled trauma patients, surgical patients, or both (18, 24, 26, 29, 30, 35), and the remaining 14 trials enrolled medical patients. Only 3 trials were performed in neutropenic patients (28, 31, 36). An IVIG dose of 1 g/kg of body weight or more was administered in 7 of the included trials (19, 25, 26, 29, 30, 34, 35), and 17 trials administered therapy for more than 2 days (17, 19, 20, 22, 24–36). Although standard therapy for the time of the study was used in all trials, the antibiotic regimen was not standardized in most of them. Co-interventions were not discussed, except in 1 trial (31) that administered a colony-stimulating factor in one half of the patients.

Death

Polyclonal IVIG use in critically ill patients was associated with a clinically and statistically significant lower mortality rate than placebo or no intervention ($n = 2621$) (risk ratio, 0.74 [95% CI, 0.62 to 0.89]; $P = 0.001$; $I^2 = 44.9\%$; $Q = 34.47$ [$P = 0.02$]) when we pooled the results from the 20 trials (Figure 2). The number needed to treat for benefit was 9 (CI, 4 to 15), which we calculated using the risk difference. Results were similar for pooled results from peer-reviewed, published trials (risk ratio, 0.72 [CI, 0.58 to 0.89]; $P = 0.002$; $I^2 = 41.9\%$; $Q = 27.52$ [$P = 0.04$]); blinded trials (risk ratio, 0.61 [CI, 0.40 to 0.93]; $P = 0.02$; $I^2 = 59.9\%$; $Q = 14.98$ [$P = 0.02$]); and the 3 high methodological quality trials (risk ratio, 0.56 [CI, 0.31 to 1.01]; $P = 0.06$; $I^2 = 0\%$; $Q = 0.59$ [$P = 0.75$]) (Figure 3). We performed additional sensitivity analyses to evaluate differences of treatment effect among studies and other potential sources of heterogeneity. The severity of sepsis by minimal inclusion criterion, dose regimen of IVIG, and duration of therapy explained most of the heterogeneity (Figure 3). Trials using severe sepsis or septic shock as inclusion criteria showed a statistically significant survival benefit (risk ratio, 0.64 [CI, 0.52 to 0.79]; $P < 0.001$; $I^2 = 0\%$; $Q = 9.64$ [$P = 0.47$]) compared with trials using sepsis as minimal inclusion criterion (risk ratio, 0.89 [CI, 0.71 to 1.10]; $P = 0.25$; $I^2 = 45.2\%$; $Q = 14.6$ [$P = 0.07$]) ($P = 0.04$ for interaction). An IVIG dose regimen of 1 gram or more per kilogram of body weight showed an increased survival benefit (risk ratio, 0.61 [CI, 0.40 to 0.94]; $P = 0.02$; $I^2 = 59.5\%$; $Q = 14.81$ [$P = 0.03$]) compared with less than 1 g/kg (risk ratio, 0.79 [CI, 0.64 to 0.97]; $P = 0.08$; $I^2 = 38.2\%$; $Q = 19.42$ [$P = 0.02$]) ($P = 0.35$ for interaction). Of more importance, duration of therapy longer than 2 days was significantly associated with this survival benefit (risk ratio, 0.66 [CI, 0.53 to 0.82]; $P < 0.002$; $I^2 = 33.6\%$; $Q = 24.1$ [$P = 0.09$]), whereas duration of therapy of 2 days or less showed no survival benefit (risk ratio, 0.98 [CI, 0.74 to

Table 2. Characteristics of the Methodological Quality of Included Trials*

Author, Year (Reference)	Type of Publication	Jadad Score†	Randomization	Blinding	Attrition Information	Follow-up Period	Industry-Funded	Intention-to-Treat	Patients Analyzed, %
Lindquist et al., 1981 (17)	Article	3	2	0	1	NR	Yes	NR	92
Just et al., 1986 (18)	Article	1	1	0	0	ICU discharge	NR	NR	NR
Jesdinsky et al., 1987 (19)	Article	2	1	0	1	NA	Yes	Yes	100
Spannbrucker, 1987 (20) et al., and Vogel et al., (21) 1988	Abstract and book chapter	1	1	0	0	NA	NR	Yes	NR
De Simone et al., 1988 (22)	Article	1	1	0	0	9 d	NR	Yes	100
Grundmann and Hornung, 1988 (23)	Article	2	1	0	1	ICU discharge	NR	Yes	100
Wesoly et al., 1990 (24)	Article	1	1	0	0	ICU discharge	NR	Yes	100
Burns et al., 1991 (25)	Article	5	2	2	1	9 d	Yes	Yes	100
Dominioni et al., 1991 (26)	Article	3	1	1	1	28 d	Yes	Yes	100
Schedel et al., 1991 (27)	Article	3	2	0	1	6 wk	Yes	NR	80
Behre et al., 1995 (28)	Article	1	1	0	0	28 d	NR	NR	100
Dominioni et al., 1996 (29)	Article	3	1	1	1	Hospital discharge	NR	Yes	100
Werdan et al., 1997 (10)	Abstract	5‡	2‡	2‡	1‡	28 d‡	Yes‡	Yes‡	95
Yakut et al., 1998 (30)	Article	3	1	1	1	NR	NR	Yes	100
Masaoka et al., 2000 (31)	Article	3	2	0	1	7 d	NR	Yes	95
Tugrul et al., 2002 (32)	Article	3	2	0	1	28 d	NR	Yes	100
Karatzas et al., 2002 (33)	Letter	2	2	0	0	28 d	NR	Yes	NR
Darenberg et al., 2003 (34)	Article	5	2	2	1	28 d	Yes	Yes	100
Rodríguez et al., 2005 (35)	Article	5	2	2	1	ICU discharge	Yes	Yes	100
Henrich et al., 2006 (36)	Article	3	2	0	1	28 d	Yes	Yes	98

* ICU = intensive care unit; NA = not available; NR = not reported.

† Based on randomization (0–2 points), blinding (0–2 points), and presence or absence of attrition information (0–1 point) (16).

‡ Based on a protocol published before the study was performed (40).

1.29]; $P = 0.86$; $I^2 = 56.7\%$; $Q = 4.62$ [$P = 0.10$] ($P = 0.03$ for interaction). Additional sources of heterogeneity among trials could not be explained by further sensitivity analyses, such as type of patients enrolled (trauma or surgical vs. medical patients), definition used for sepsis (strict ACCP/SCCM criteria vs. other definitions), baseline immune status (neutropenic patients vs. nonneutropenic patients), and timing of administration of IVIG (at any time vs. day 0).

Length of Stay in the ICU

Eight trials reported data on patients' length of stay in the ICU (18, 23, 24, 26, 29, 30, 32, 35). In 1 trial (32), researchers presented the ICU length of stay as a median time (29 days [range, 3 to 89 days] in the IVIG group vs. 22 days [range, 3 to 85 days] in the control group; $P = 0.35$), and another trial presented means with no corresponding measures of dispersion (21 days in the IVIG group vs. 16.9 days in the control group among survivors; $P > 0.05$) (18). One trial (26) was not used for the pooled analysis because included data from another trial could not be extracted (29). Thus, only 5 trials (23, 24, 26, 30, 35)

($n = 239$) presented the necessary data to perform a pooled analysis for this outcome. No statistically significant difference between the 2 groups was observed (mean reduction, 0.24 day [CI, 2.59 to 2.11 days]; $P = 0.84$; $I^2 = 0\%$; $Q = 2.95$ [$P = 0.56$]).

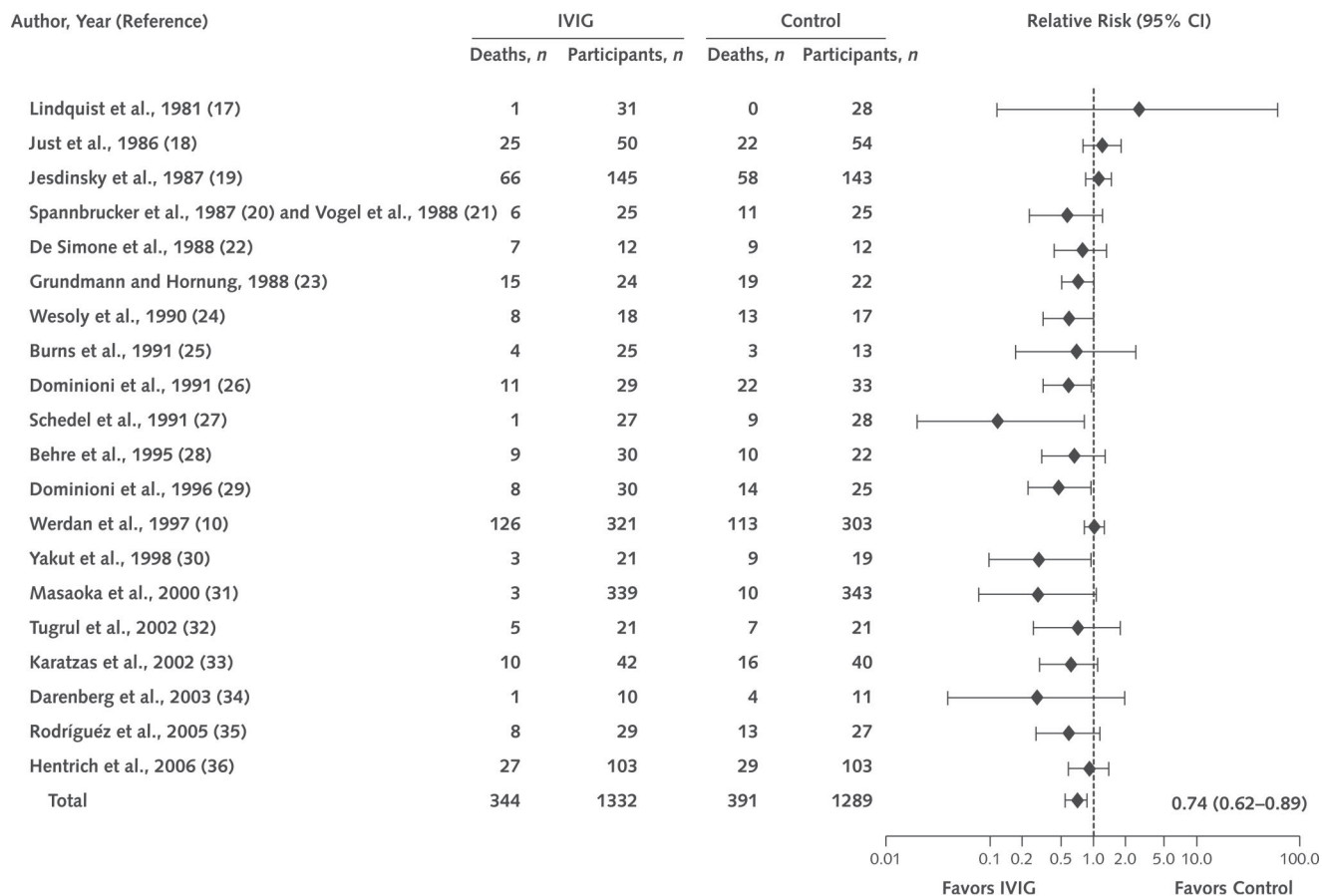
Days of Mechanical Ventilation

Only 2 trials (23, 24) reported data on duration of mechanical ventilation ($n = 79$). Pooled results of these trials showed no statistically significant reduction of days of mechanical ventilation (mean reduction, 0.32 day [CI, –6.76 to 6.12 days]; $P = 0.92$; $I^2 = 53.5\%$; $Q = 2.15$ [$P = 0.14$]) for patients receiving IVIG therapy.

Publication Bias

We generated a funnel plot of effect size versus standard error from each study to evaluate the presence of potential publication bias with regard to the meta-analyses performed in our review. We saw no clear suggestion of heterogeneity or possible publication bias on the funnel plot.

Figure 2. Difference in the number of deaths between patients who received intravenous immunoglobulin (IVIG) and those who received placebo or no intervention.



DISCUSSION

In our systematic review, polyclonal IVIG used as an adjuvant therapy in critically ill adult patients with sepsis reduced death compared with placebo or no intervention. Moreover, we consistently observed this survival benefit in sensitivity analyses. The overall survival benefit attributed to the use of polyclonal IVIG from published trials of patients with sepsis, severe sepsis, or septic shock generated a number needed to treat for benefit of 9 (CI, 4 to 15), similar to that for activated protein C. Considering the high mortality rate associated with severe sepsis, the use of IVIG could save an additional 20 000 lives every year in the United States (1, 41). The estimated cost for a treatment of 1 g/kg in a patient who weighs 70 kg would be approximately \$4000 to \$5000. Treatment with activated protein C costs approximately \$10 000. We found that dose regimens of 1 gram or more per kilogram, duration of therapy longer than 2 days, and the use of the treatment in more severely ill patients were associated with an increased survival benefit.

Polyclonal IVIG has few absolute treatment indica-

tions but several off-label indications (8). For the treatment of sepsis, IVIG is considered to be an accepted adjuvant by the U.S. Food and Drug Administration for group A streptococcal toxic shock syndrome (7). However, we identified more trials performed in a general population of patients affected by sepsis than trials performed in patients with specific infections. Therefore, our meta-analysis provides evidence supporting the use of IVIG in a general population of critically ill patients with sepsis.

We found no significant differences between the IVIG group and the control group in ICU length of stay and days of mechanical ventilation in pooled results of a few trials. This may be due in part to the relatively small number of studies that reported these surrogate outcomes. Furthermore, because death from sepsis is seen early in the course of the disease, the higher mortality rate observed may have shortened the mean ICU length of stay and days of mechanical ventilation in the control group.

Researchers have attributed adverse effects, such as acute renal failure, aseptic meningitis, anaphylaxis, thromboembolic events, and viral infections, to the use of IVIG

(42–44). However, severe adverse effects are rare if not anecdotal (42). In the 6 trials included in our meta-analysis that reported adverse effects, most reactions were mild or moderate in severity. When severe adverse reactions were reported (shock or dyspnea), they were more likely to be secondary to the disease than to the treatment regimen (17, 31, 34). Thus, the incidence of severe adverse reactions seems to be lower than the incidence of bleeding associated with activated protein C. No reaction was associated with death. However, the risk for severe adverse reactions might have been underestimated because the studies were not designed to specifically determine their incidence.

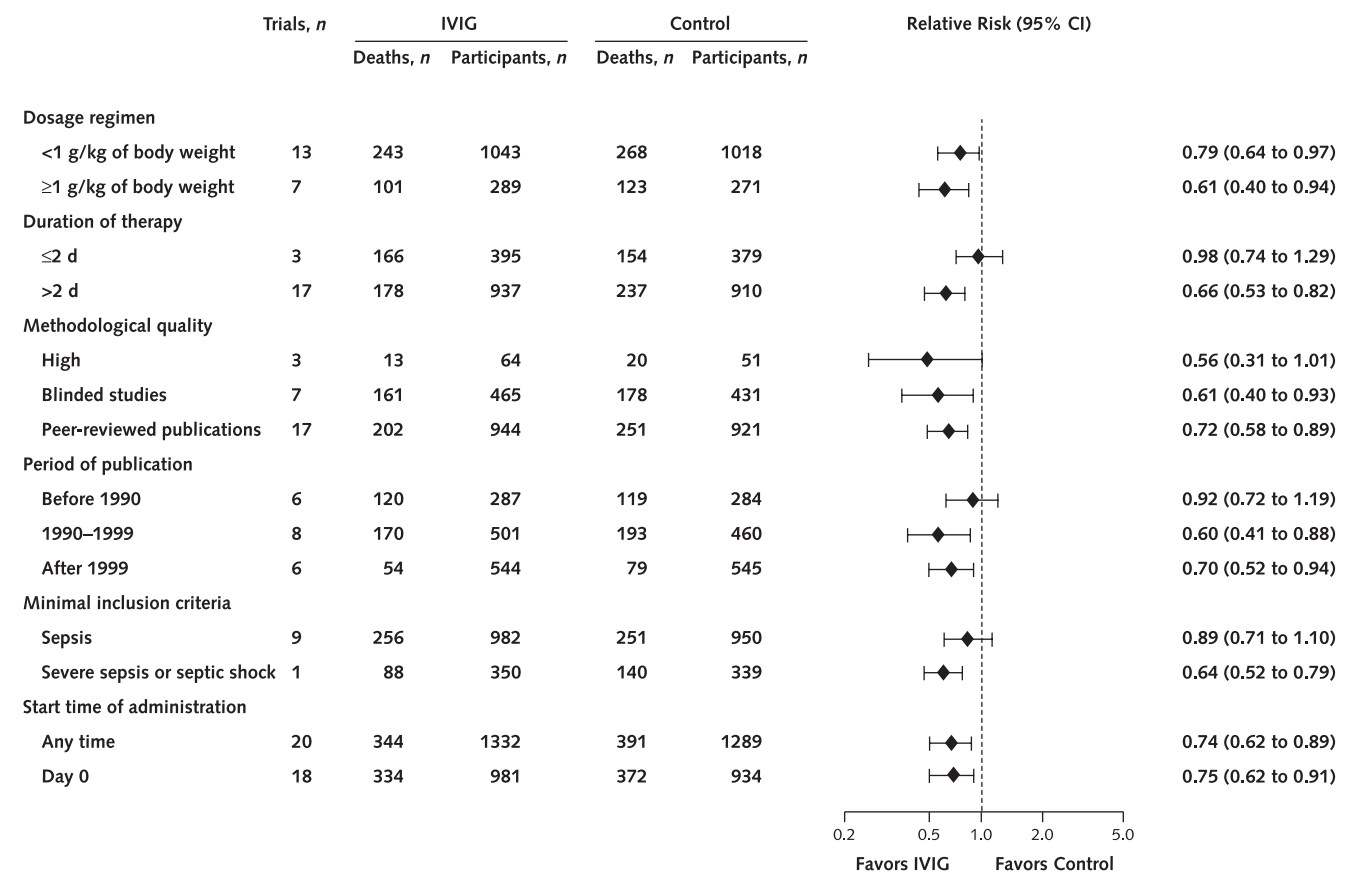
The results obtained in our systematic review are consistent with a previous meta-analysis of 6 published trials performed by Alejandria and colleagues (9). All trials included in their meta-analysis also met inclusion criteria for our review (18, 22–24, 27, 29). Several plausible reasons may explain why we identified 13 more trials than Alejandria and colleagues. First, 4 trials (20, 28, 30, 31) included in our review were not referenced in MEDLINE and were found only by searching citations used in other trials. Second, we had no language restriction and this allowed us to identify 5 trials published in languages other than English

(18, 20, 24, 30, 31). Finally, the systematic review by Alejandria and colleagues excluded some trials because of low methodological quality. Our approach was to verify methodological quality by obtaining additional information on protocol design from study authors and by performing sensitivity analyses to explore the effect of quality on potential inferences rather than to exclude trials. Alejandria and colleagues' findings were consistent with those of our systematic review despite the fewer trials.

A recent meta-analysis by Pildal and colleagues (11) observed no survival benefit with the use of polyclonal IVIG in sepsis compared with placebo or no intervention. Their meta-analysis (21 studies) included 16 of the 19 trials included in our systematic review. However, overall results of these trials performed in adults were pooled with results of pediatric and neonatal trials, hence broadening their study population to a different collection of individuals. The immune response to sepsis is different in neonates.

One large multicenter trial by Werdan and colleagues (10) observed no survival benefit with the use of IVIG in sepsis. However, close to 10 years after its completion, their trial has not been published. The methodological quality of the trial, which could only be assessed via a

Figure 3. Death according to treatment regimen, severity of disease, or methodological quality.



previously published protocol (40), may have deviated from exact trial conduct (45, 46). Without the benefit of peer review and a full report of the results, we could not properly scrutinize the quality of the trial and could not define it as being of high methodological quality.

Methodological limitations of primary studies is the major limitation of our systematic review. Most trials included in our meta-analysis predated the definitions of sepsis, severe sepsis, and septic shock that was standardized in the early 1990s for research purposes (13). However, the overall mortality rate (nonweighted) was 30% in the control group (Figure 2), a lower mortality rate than that currently observed in patients with septic shock but similar to that of the population enrolled in the PROWESS trial (3). Thus, despite the use of different definitions for sepsis, the sample studied in our meta-analysis was probably representative of the actual population of patients with severe sepsis. Of interest, negative trials were conducted in a broad sample of patients with sepsis, and most positive trials were conducted in a sample of patients with severe sepsis or septic shock (Figure 3).

Most studies were published before many recent trials that have modified the care and outcome of critically ill adult patients with sepsis (2, 3, 47–49). Introduction of new antibiotics and activated protein C treatment (3) and the concept of early goal-directed therapy (2) have modified the standards of treatment over the past decade. For most trials in our review, these standards were not applied during the study period. Thus, the effect of IVIG therapy in this setting is unknown. However, when results of trials are pooled according to their period of publication, the more recent trials were associated with an increased survival benefit compared with the earlier trials (Figure 3). New standards of care and potentially better quality of product may be responsible for this observed difference. Finally, despite our finding of no clear evidence of publication bias, such bias remains a possibility because of the inadequacies of current statistical techniques.

In summary, we observed a 26% survival benefit in the 20 trials conducted in 2621 patients with sepsis that evaluated the use of IVIG therapy. The benefits of therapy were most prominent in more severely ill patients with sepsis when treatment was given at higher doses for longer periods. If the survival benefit that we found is true, the magnitude of the benefit, considering a number needed to treat for benefit in the range of 9, the cost of therapy, and the incidence of severe adverse reactions, compares favorably with that of the use of activated protein C. Considering the many limitations of the current literature, limited available information from a large trial (10), potential benefit in more severely ill patients, and potential effect of dosage and duration of therapy, we believe that polyclonal IVIG should be evaluated in well-defined populations at high risk for death who are receiving current standard of therapy for sepsis.

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