Evaluation of the Effect of Intravenous Immunoglobulin Dosing on Mortality in Patients with Sepsis: A Network Meta-analysis

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ABSTRACT

Purpose: Intravenous immunoglobulin (IVIG) has been proposed as an adjunctive therapy for sepsis. Related systematic reviews and meta-analyses of IVIG in sepsis indicate that IVIG can reduce the mortality of sepsis in adults. However, the effective dose of IVIG has not been clearly determined to date. We aimed to conduct an updated meta-analysis and use a network meta-analysis to elucidate the efficacy of IVIG dosing regimens in sepsis treatment.

Methods: We searched PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE for articles published on or before February 14, 2019. We performed a direct meta-analysis to update a previous meta-analysis of the effects of IVIG therapy on mortality in adult patients with septic shock and a network meta-analysis to evaluate the efficacy of IVIG dosing regimens in sepsis treatment.

Findings: Compared with the control treatment, the IVIG treatment reduced the all-cause mortality of patients with sepsis (odds ratio = 0.61; 95% CI, 0.41−0.92; $P = 0.018$), but significant heterogeneity was found across the studies ($I^2 = 45.0\%$; $P = 0.04$). Regarding the IVIG dosage regimens, the highest total dose range (1.5−2 g/kg) was the optimal dose of administration (surface under the cumulative ranking curve = 84.7%).

Implications: On the basis of the available data, IVIG treatment is likely to reduce the all-cause mortality of patients with sepsis, and the highest total dose range (1.5−2 g/kg) is likely the optimal dose of administration. (*Clin Ther*. 2019;41:1823−1838) © 2019 Published by Elsevier Inc.

Key words: intravenous immunoglobulin, network meta-analysis, optimal dose, review, sepsis.

INTRODUCTION

Sepsis is defined as "life-threatening organ dysfunction due to a dysregulated host response to infection.[1]" The development of sepsis results from a complex interaction between the infecting microorganism and the host response. In fact, sepsis is associated with altered homeostasis characterized by the activation of inflammation over several years. This increased inflammatory response is defined as systemic inflammatory response syndrome.[2] The incidence rate of sepsis is 535 cases per 100,000 person-years, and the hospital mortality rate is 25% to 30%.[3] Sepsis is a serious, life-threatening disease. Therefore, the treatment of sepsis has a significant effect on survival.

Intravenous immunoglobulin (IVIG) is a fractionated blood product obtained from pooled human plasma that is widely used for replacement therapy in patients with primary immunodeficiency.[4] IVIG has anti-inflammatory actions in addition to its function as a replacement for deficient immunoglobulin and its immunomodulatory actions.[4] IVIG was first used in the 1980s as an adjuvant therapy for sepsis, and some randomized clinical trials (RCTs) have been published. All previous meta-

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analyses suggest that IVIG significantly reduces the mortality of sepsis in adults.[5,6] Considering the effectiveness of IVIG as sepsis treatment, some guidelines recommend the use of IVIG for the treatment of sepsis, which is caused by a special minority of bacteria. The Department of Health of the United Kingdom published *Clinical Guidelines for Immunoglobulin Use* in 2011.[7] In this guideline, necrotizing staphylococcal sepsis and staphylococcal or streptococcal toxic shock syndrome are blue recommendations (suggesting that IVIG treatment has a reasonable evidence base but requires the prior approval of an immunoglobulin assessment panel). Another set of guidelines, *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia*,[4] recommends the use of IVIG treatment for indications, including sepsis (the quality of the related evidence is classified as guideline 2a). However, the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*[8] does not recommend the use of IVIG for the treatment of septic (weak recommendation based on low evidence quality). The efficacy of IVIG in the treatment of sepsis remains controversial, and all previous RCTs used varying IVIG dosing regimens for the treatment of sepsis. Dose optimization studies have not been reported, and questions remain regarding the most effective IVIG dosing regimen. Hence, when prescribing IVIG, practitioners are faced with a myriad of different dosages, posing a challenge to clinical decision making. We performed a meta-analysis to assess the efficacy of IVIG in the treatment of sepsis and a network meta-analysis, which allows for the integration of direct evidence with indirect evidence from multiple treatment comparisons for the estimation of the interrelations across all treatments, to evaluate the efficacy of IVIG dosing regimens for sepsis treatment.

METHODS

Search Strategies and Selection Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for network meta-analyses of health care intervention studies.[9] PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Ovid EMBASE were searched from inception to February 14, 2019. The search strategy used keywords and medical subject headings. The key search terms included *immunoglobulins, intravenous*; *immunoglobulins*; *intravenous immune globulin**; *immunoglobulin**; *IVIG*; *sepsis*, *shock, septic*; *septicemia*; *severe sepsis*; *septicem**; *septicaem**; and additional text words in combination with an established search strategy for PubMed.[10] Search restrictions of English language and RCTs were used. Detailed information regarding the search strategy is provided in Supplement 1.

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to determine the inclusion and exclusion criteria. Details regarding the inclusion criteria[11–13] are given in Table I. The exclusion criteria were as follows: any indefinite diagnosis of sepsis or septic shock, treatment with any other monoclonal immunoglobulin, or an unreported number of doses or mortality.

Study Selection and Data Extraction

Two investigators (Y.Y. and X.Y.) independently assessed the trials for eligibility and extracted information, including the study design, patient characteristics, detailed treatment protocols (doses and treatment duration), and outcomes (all-cause mortality), into an electronic database. Disagreement was resolved by a joint review of the article to reach consensus. In cases of reports from the same trial at different follow-up periods, the data from the most recent report were used in the analysis. The risk of bias in individual studies was assessed independently by the reviewers using the same risk of bias assessment tool for randomized trials from the Cochrane Handbook.[14] A risk of bias graph was generated to display the ratings of bias as high risk, unclear risk, or low risk. The risk of bias assessment was performed using Review Manager 5.3 (Oxford, UK; The Cochrane Collaboration).

Statistical Analysis

Direct Meta-analysis

We calculated the odds ratios (ORs) and 95% CIs of the treatments (IVIG group and control group), and all-cause mortality was the outcome. We calculated the pooled estimates of the meta-analysis between the intervention groups by using a random-effects model to adequately account for the additional uncertainty

Table I. Details of inclusion criteria.

Participants	Adult patients (mean age, ≥18 years) The diagnostic criteria for sepsis: (1) Patients who fulfilled ≥2 of the following SIRS criteria[11,12]: (1) temperature >38°C or < 36°C; (2) heart rate >90/min; (3) respiratory rate >20/min or $Paco_2$ <32 mm Hg; (4) white blood cell count >12 × 10^9/L or <4 × 10^9/L or >10% immature white blood cells (2) Patients with life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was identified as an acute change in total sequential organ failure assessment score >2 points consequent to the infection.[13]
Interventions	Any types of IVIG for treatment of sepsis or septic shock.
Control	Placebo, no immunoglobulin, other types of IVIG, or other IVIG administration for treatment of sepsis or septic shock
Outcomes	All-cause mortality
Studies	Randomized clinical trial

IVIG = intravenous immunoglobulin; SIRS = systemic inflammatory response syndrome.

associated with between-study variability in the effect of different treatments, and statistical heterogeneity was estimated using the χ^2 test (I^2) (I^2 > 25% indicated low heterogeneity, I^2 > 50% indicated at least moderate heterogeneity, and I^2 > 75% indicated high heterogeneity).[15] To assess publication bias, we used the trim and fill method in a sensitivity analysis.[16] We performed a subgroup analysis based on the risk of bias and the study publication year.

Network Meta-analysis

To evaluate the effect sizes of the different IVIG dosing regimens, we also performed a network meta-analysis with an extension of frequentist random-effects models from indirect evidence. According to the total dose of IVIG, we formed 4 groups: group A (0.45−0.49 g/kg), group B (0.5−0.99 g/kg), group C (1−1.49 g/kg), and group D (1.5−2 g/kg). The different groups of IVIG were treated as separate nodes. To rank the treatments based on efficacy, we calculated the probabilities of the surface under the cumulative ranking curves (SUCRAs) (cumulative probabilities vs rank). SUCRAs can illustrate the outcome percentages of each treatment relative to the ideal treatment. In the SUCRA, a value of 1 indicates that a treatment is certain to be the best treatment, and a value of 0 indicates the worst treatment.[17] A network meta-analysis was performed with the mvmeta command in Stata, version 12.0 (StataCorp, College Station, Texas) as described by White et al.[18] We derived the raw event rates from individual studies and constructed 2 × 2 tables based on the raw numbers of events and total populations of the trials. The pooled estimates of the ORs with 95% CIs were calculated for these categorical outcomes.

RESULTS

Study Characteristics

In total, 1546 studies were identified in the 3 electronic databases; of these studies, 1374 were excluded after screening the title and abstract, and 57 studies were excluded after screening the full text. Finally, 13 RCTs[19−31] involving a total of 1041 patients randomly assigned to receive IVIG or placebo treatment were included in the meta-analysis (Figure 1).

The characteristics of the 13 included RCTs are summarized in Table II and Table III. In all RCTs, the intervention (IVIG) and control treatments were administered as adjunctive therapy to standard care. Six RCTs[19,23,24,26,28,31] compared standard polyclonal IVIG treatment with a control treatment (no intervention or placebo), and 7 trials[19,21,22,25,27,29,30] compared IgM-enriched polyclonal IVIG treatment with a control treatment (no intervention or placebo).

The total dosage of IVIG among the trials ranged from 0.45 to 2 g/kg, and the treatment duration

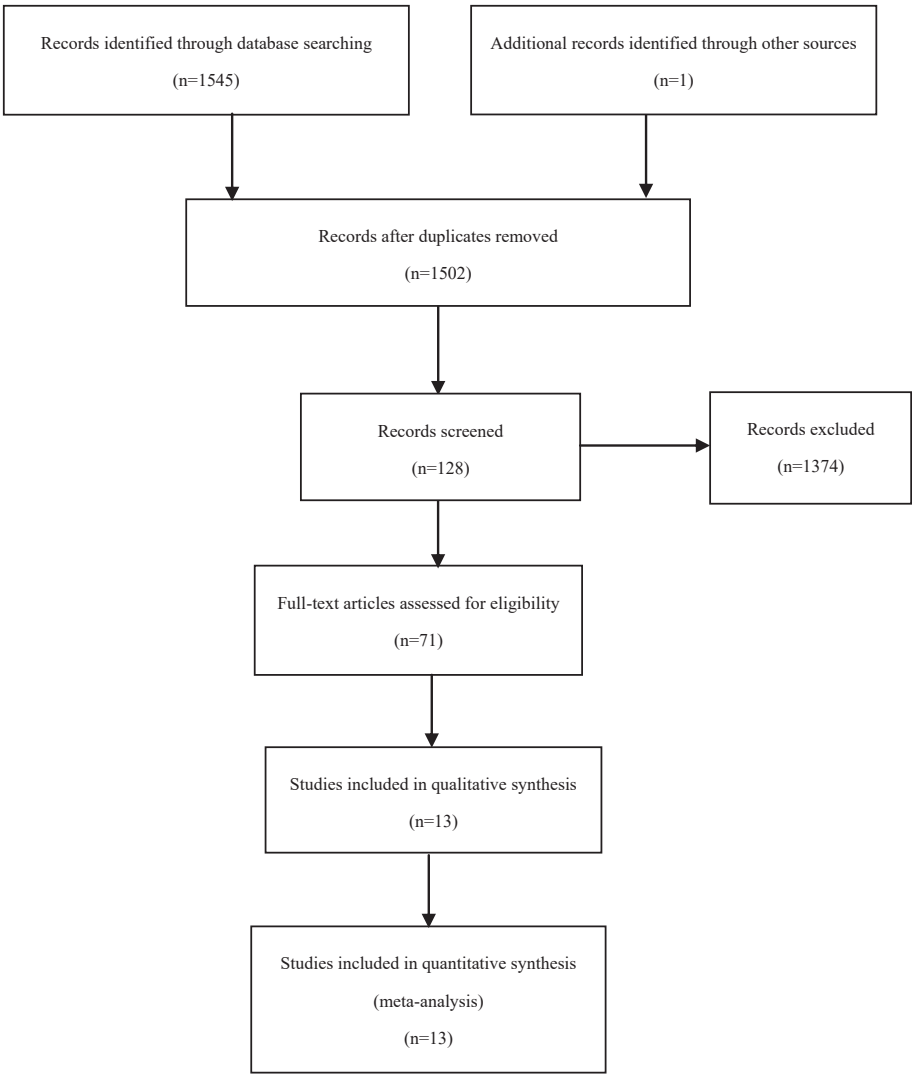

Figure 1. Search flow diagram.

ranged from 2 to 5 days. The mean age of the patients ranged from 37 to 65.9 years, and the percentage of male patients ranged from 14.3% to 70.6%. Six RCTs[20–23,27,29,31] reported the severity of illness, and the severity of illness was similar between the intervention group and the control group. Seven RCTs[19,20,22,24,25,27,31] reported the detection of microorganisms, 3[19,20,25] of which described the microorganisms detected overall and 4[22,24,27,31] of which described the microorganisms detected in the control and intervention groups separately; the microorganisms detected in the 2 groups were similar.

Risk of Bias

Overall, the results indicated an acceptable risk of bias among these RCTs as summarized in Figure 2 and Figure 3. Of the 13 trials, 10[20–23,25–30] (76.9%) were judged to have a low risk of bias for randomization methods, 9[20–23,25,26,28–30] (69.2%) for concealment allocation, 9[19–23,26,29–31] (69.2%) for blinding, 10[19–27,30] (76.9%) for incomplete outcome data, 8[20–23,25,27–31] (61.5%) for selective reporting, and 10[19,20,22–24,26,27,29–31] (76.9%) for other bias. Most studies reported the differences in dropouts between the treatment groups and the

Table II. Description of interventions and dosing regimens.

Study	Intervention	Control	IVIG Dosing Regimen	Total Dose, g/kg	Duration, d
Hentrich et al,[19] 2006	IgM-enriched IVIG (Pentaglobin, Biotest Pharma, Dreieich, Germany)	5% Human albumin	1300 mL for 72 hours: 200 mL initially (0.5 mL/min), then 11 infusions of 100 mL every 6 hours	0.93	3
Darenberg et al,[20] 2003	IVIG (Endobulin, Baxter, Deerfield, IL) (solution)	1% Human albumin	1 g/kg on day 1 then 0.5 g/kg on days 2 and 3	2	3
Rodríguez et al,[21] 2005	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	5% Human albumin	7 mL/kg daily for 5 days	1.75	5
Toth et al,[22] 2013	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	0.9% Sodium chloride	5 mL/kg for 3 days	0.75	3
Werdan et al,[23] 2007	5% Solution of IVIG (Polyglobin, Bayer Biological Products, Leverkusen, Germany)	0.1% Human albumin	0.6 g/kg on day 0 and 0.3 g/kg on day 1	0.9	2
De Simone et al,[24] 1988	IVIG (Sandoglobulin, Sandoz Pharmaceutical Corp, Trento Italy)	No treatment	0.4 g/kg on day 1 and 0.2 g/kg after 48 h and 0.4 g/kg after 5 days	1	5
Schedel et al,[25] 1991	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	No treatment	600 mL on day 1 and 300 mL on days 2 and 3	0.86	3
Burns et al,[26] 1991	IVIG (Sandoglobulin, Sandoz Pharmaceutical Corp)	Human albumin	400 mg/kg for 3 days	1.2	3
Tugrul et al,[27] 2002	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	No treatment	5 mL/kg for 3 days	0.75	3
Lindquist et al,[28] 1981	IVIG (Gamma-Venin)	No treatment	0.15 g/kg for 3 days	0.45	3
Karatzas et al,[29] 2002	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	No treatment	5 mL/kg for 3 days	0.75	3
Behre et al,[30] 1995	IgM-enriched IVIG (Pentaglobin, Biotest Pharma)	5% Human albumin	10 g then 5 g every 6 h for 72 h	0.93	3
Dominion et al,[31] 1996	IVIG (Sandoglobulin, Sandoz Pharmaceutical Corp)	5% Human albumin	0.4 g/kg on day 0, 0.4 g/kg on day 1, and 0.2 g/kg on day 5	1	5

IVIV = intravenous immunoglobulin.

Table III. Baseline patient characteristics.

Study	Intervention					Control					Time of Antibiotic Therapy	Microorganisms	Adverse events	Mortality Outcome
	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)				
Hentrich et al,[19] 2006	103	63 (61.2)	48.4	NR	27 (26.2)	103	58 (56.3)	51.0	NR	29 (28.1)	During the study period, standard sepsis therapies were used, immediate initiation or modification of broad-spectrum antimicrobial therapy	Gram-positive bacteria: 42; gram-negative:35; fungi: 13; both gram-positive and gram-negative: 16	5 Patients had adverse events likely related to the use of immunoglobulin (allergic reaction: 3; erythema: 1; nausea and vomiting: 1)	28 Days
Darenberg et al,[20] 2003	10	4 (40.0)	51.3	SAPS II, 53; SOFA score, 11.0	1 (10.0)	11	6 (54.5)	52.6	SAPS II, 51; SOFA score, 11.0	4 (36.4)	The total period of antibiotic treatment was standardized to at least 14 days	Group A streptococcal: 13; group B streptococci-positive *Staphylococcus aureus*: 3; *Pseudomonas aeruginosa*: 2	Reported were 6 severe adverse events and 12 adverse events; none of the events were reported to be related to the study drug	28 Days
Rodríguez et al,[21] 2005	29	11 (37.9)	61.3	SAPS II, 16.1	8 (27.6)	27	9 (33.3)	65.9	SAPS II, 15.2	13 (48.1)	Antibiotic therapy was left to the discretion of each center	NR	NR	ICU
Toth et al,[22] 2013	16	8 (50)	56.0	SAPS II, 26	12 (75.0)	17	4 (23.5)	60.0	SAPS II, 25	12 (70.6)	NR	IVIG group/control group: MRSA: 7/7; *Escherichia coli*: 4/3; *Candida albicans*:1/1; UK: 4/6	NR	28 Days
Werdan et al,[23] 2007	321	239 (74.5)	57.2	APACHE II score, 27.6; sepsis score, 18.4; sepsis criteria, 5.7; SIRS criteria, 3.19	126 (39.3)	303	202 (66.7)	57.7	APACHE II score, 28.0; sepsis score, 18.3; sepsis criteria, 5.6; SIRS criteria, 3.18	113 (37.3)	Decisions about antimicrobial drug therapy were made by the patient's attending physicians and were not dictated by the study protocol	NR	6 Adverse events in 6 patients of the placebo group and 13 adverse events in 11 patients of the IVIG group	28 Days
De Simone et al,[24] 1988	12	5 (41.7)	45	NR	7 (58.3)	12	7 (58.3)	45	NR	9 (75.0)	NR	(Blood) IVIG group/control group: gram-positive bacteria: 5/6; gram-negative:1/1	NR	70 Days

Table III. (*Continued*)

Study	Intervention					Control					Time of Antibiotic Therapy	Microorganisms	Adverse events	Mortality Outcome
	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)				
Schedel et al,[25] 1991	27	15 (55.6)	46	NR	1 (3.7)	28	14 (50.0)	37	NR	9 (32.1)	NR	*P aeruginosa*: 15; *E coli*: 12; *Enterobacter* spp: 8; *Proteus* spp: 6; *Klebsiella pneumonia*: 5; *Serratia marcescens*: 2; *Citrobacter freundii*: 8; *Morganella morganii*: 1	None of the events were reported to be related to the study drug	42 Days
Burns et al,[26] 1991	19	NR	61.5	NR	4 (21.1)	19	NR	59.8	NR	3 (15.8)	NR	NR	NR	9 Days
Tugrul et al,[27] 2002	21	12 (57.1)	42	APACHE II score, 10.5; SOFA score, 5.0; GCS score, 14.2	5 (23.8)	21	10 (47.6)	49.3	APACHE II score, 14.0; SOFA score, 5.7; GCS score, 12.9	7 (33.3)	NR	IVIG group/control group: *P aeruginosa*: 5/5; MRSA: 9/5; *Acinetobacter* sp: 1/4; *Klebsiella pneumoniae*: 1/1; *Enterobacter* sp: 1/0; *Stenotrophomonas maltophilia*: 1/0; *E coli*: 0/1; UK: 3/5	NR	28 Days
Lindquist et al,[28] 1981	31	20 (64.5)	39.2	NR	1 (3.2)	38	14 (36.8)	42.1	NR	0 (0)	All patients received antibiotic therapy according to hospital routine, which remained constant throughout	NR	Shock: 2; Rigor, chills, and somnolence; rigor, chills, and elevation of temperature; rigor, chills, and elevation of vomiting	14 Days
Karatzas et al,[29] 2002	34	NR	50.5	APACHE II score, 21.3	8 (23.5)	34	NR	50.7	APACHE II score, 23.5	14 (41.2)	NR	NR	NR	28 Days
Behre et al,[30] 1995	30	NR	50.0	NR	9 (30.0)	22	NR	55.0	NR	10 (45.5)	NR	NR	NR	28 Days

(*continued on next page*)

Table III. (*Continued*)

Study	Intervention					Control					Time of Antibiotic Therapy	Microorganisms	Adverse events	Mortality Outcome
	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)	Total No. of Patients	Men, No. (%)	Age, Mean (SD), y	Severity of Illness	Mortality, No. (%)				
Dominion et al,[31] 1996	57	40 (70.2)	55.0	Sepsis score, 23	19 (33.3)	56	40 (71.4)	57.0	Sepsis score, 23	36 (64.3)	NR	IVIG group/control group: *Pseudomonas*: 38/43; *Staphylococcus*: 35/47; *E coli*: 24/22; *Enterobacter*: 10/7; *Enterococcus*: 11/6; *Streptococcus*: 9/9; *Proteus*: 14/5; *Serratia*: 5/5; *Bacteroides*: 1/3; *Fusobacterium*: 0/2; *Clostridium*: 0/2; *Klebsiella*: 9/2; *Acinetobacter*: 1/1; *Haphnia alvei*: 1/0; *Salmonella* spp: 0/2; *Cytobacter*: 1/0; *M morganii*: 1/1; *Xanthomonas mahophilta*: 0/1; *Candida*: 21/7	None of the events were reported to be related to IVIG	ICU

APACHE = Acute Physiology, Chronic Health Evaluation; GCS, Glasgow Coma Scale; ICU = intensive care unit; IVIV = intravenous immunoglobulin; MRSA = methicillin-resistant *Staphylococcus aureus*; NR = not reported; SAPS = Simplified Acute Physiology Score; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment; UK = Unknown.

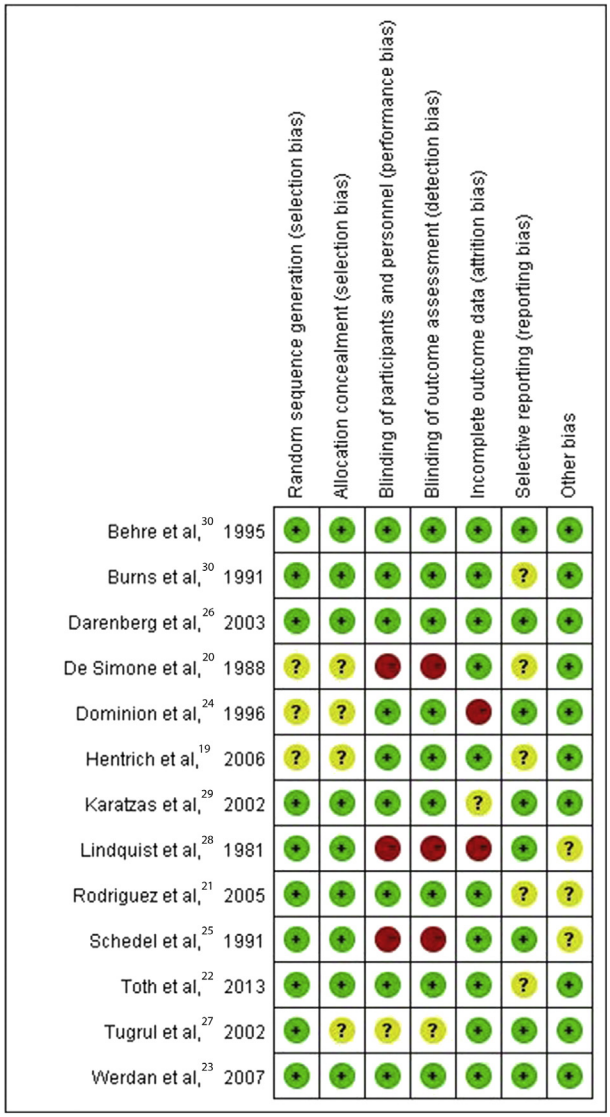

Figure 2. Methodologic quality summary: a review of the authors' judgments of each. methodologic quality item for each included study.

reasons for patient withdrawal, except for 2 studies[28,31] with incomplete outcome data rated as a high risk of bias and 1 study[29] with incomplete outcome data rated as unclear risk of bias.

Direct Meta-analysis

Figure 4 shows the results of the direct meta-analysis. The meta-analysis using a random-effects model found that IVIG could reduce mortality (OR = 0.61; 95% CI, 0.41−0.92; P = .018) but with some degree of heterogeneity across the trials (I^2 = 45.0%; P = 0.04).

The results of the sensitivity analysis using the trim and fill method are shown in Figure 5. The funnel plot shows asymmetry, and the combined effect after the trim and fill is as follows: OR = 1.02; 95% CI, 0.82−1.26. When only the 3 RCTs[20,23,30] with low risk of bias were included, IVIG reduced mortality of sepsis, but the difference was not significant (OR = 0.77; 95% CI, 0.36−1.62; P = 0.485) (Supplement 3). The subgroup analysis based on the publication year of the studies is given in Supplement 4. The results indicate that when only studies published before 2000 were included, IVIG reduced the mortality of sepsis (OR = 0.44; 95% CI, 0.22−0.91; P = 0.026), and a significant difference was observed; when only studies published after 2000 were included, IVIG still reduced the mortality of sepsis (OR = 0.84; 95% CI, 0.60−1.17; P = 0.299), but the difference was not significant.

Network Meta-analysis

The direct meta-analysis indicated that IVIG was effective in reducing all-cause mortality in patients with sepsis. However, among all studies, the total IVIG dose ranged from 0.45 to 2 g/kg, and the duration of treatment ranged from 2 to 5 days. Thus, a network meta-analysis was applied to reveal the optimal total IVIG dose for sepsis treatment.

According to the range of the total IVIG doses, the RCTs were divided into the following 4 groups: group A (0.45−0.49 g/kg), group B (0.5−0.99 g/kg), group C (1−1.49 g/kg) and group D (1.5−2 g/kg). The network plot of sepsis among the different total doses of the IVIG treatment regimens is given in Supplement 2. The pooled ORs and 95% CIs of the treatment efficacy among the different groups in the network meta-analysis are given in Table IV. Compared with the control group, group C had significantly reduced mortality from sepsis in adults (OR of group C vs control = 0.42; 95% CI, 0.19−0.93), and groups B and D had reduced mortality from sepsis but no significant difference. Group A had no mortality reduction (OR of group A vs control = 3.79; 95% CI, 0.14−101.22) compared with the control group. Group D had a higher efficacy in reducing mortality than groups B and C

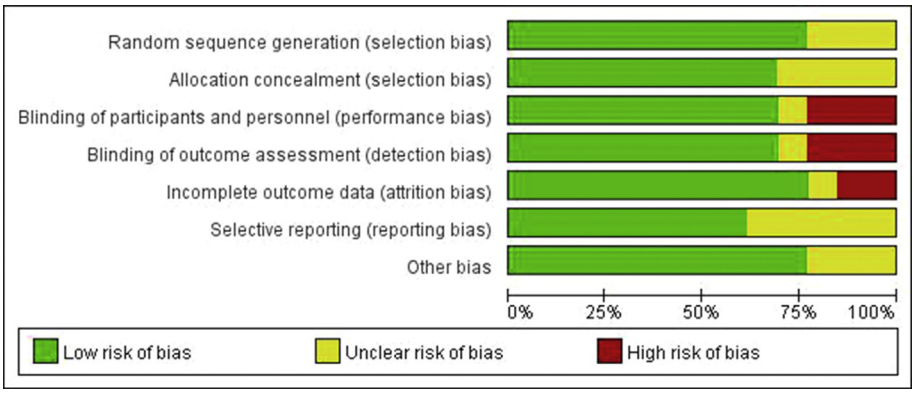

Figure 3. Risk of bias graph: a review of the authors' judgements of each risk of bias item presented as percentages across all included studies.

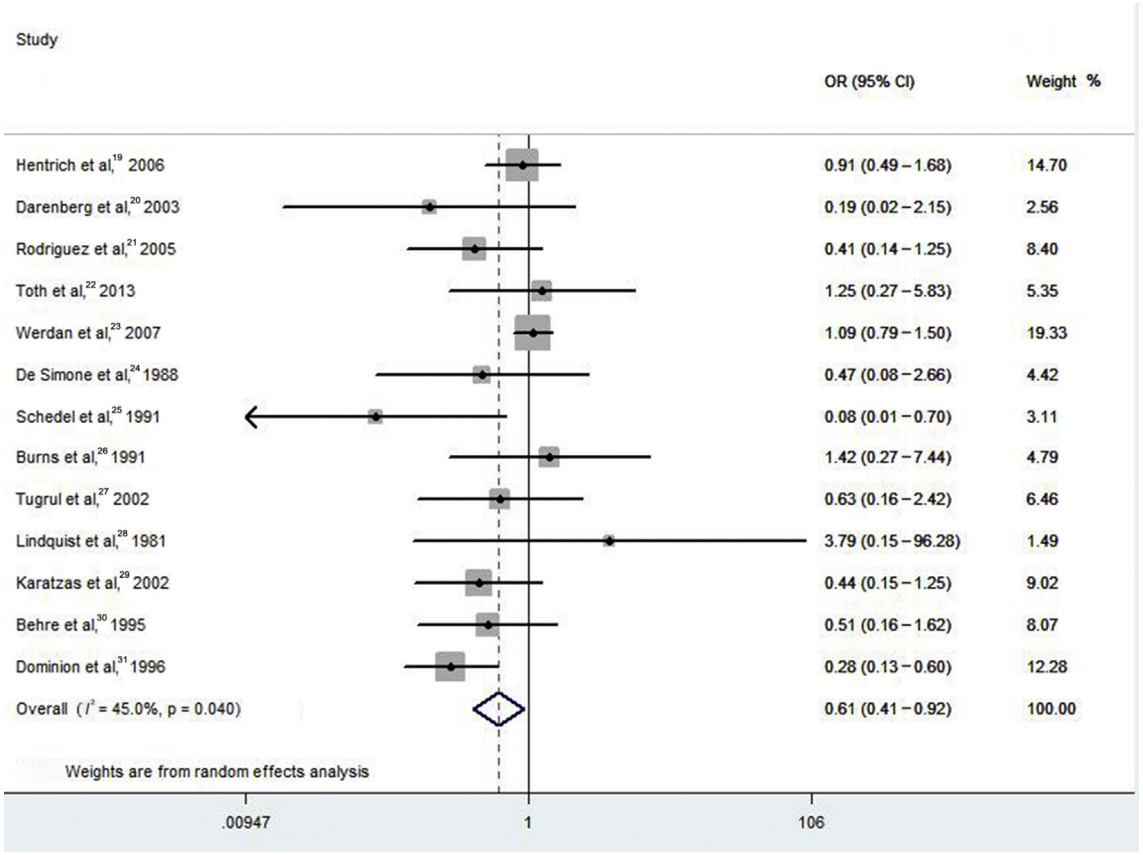

Figure 4. Results of the direct meta-analysis. Random-effects model to estimate the effect of intravenous immunoglobulin. Overall odds ratio [OR] = 0.61 (95% CI, 0.41−0.92; $P = 0.018$).

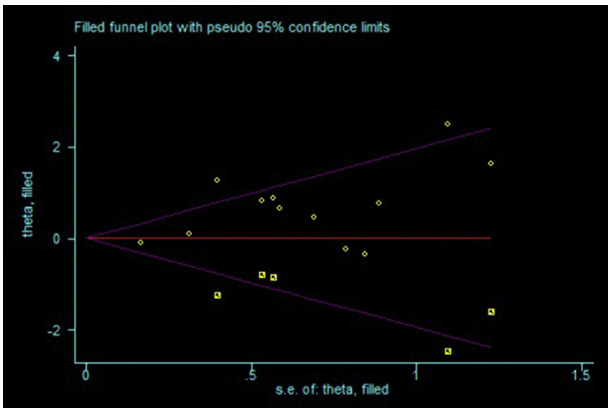

Figure 5. Results of the the sensitivity analysis using the trim and fill method. circles indicate the analyzed studies, boxes indicate the trimmed studies. the combined effect after trim and fill is: OR: 1.018; 95% CI: 0.823, 1.258.

(OR of group D vs group B = 0.46, 95% CI, 0.14−1.53; OR of group D vs group C = 0.85, 95% CI, 0.21−3.38).

The SUCRAs of the treatment efficacy are shown in Figure 6. The highest ranked intervention was observed in group D, with a SUCRA of 84.7%, representing the best clinical outcomes. The order of the remaining groups was as follows: group C (SUCRA = 78.5%), group B (SUCRA = 48.9%), the control group (SUCRA = 25.1%), and group A (SUCRA = 12.8%).

Adverse Events

Six studies[19,20,23,25,28,31] reported adverse events (Table III). Only 3[19,23,28] of those reported adverse events that were related to the study drugs, and drug-related adverse events were allergic reaction, erythema, nausea, vomiting, shock, rigor, chills, somnolence, elevation of temperature, and others.

DISCUSSION

Sepsis is a syndrome characterized by physiologic, pathologic, and biochemical abnormalities that is induced by a systemic inflammatory response to infection. Sepsis remains a leading cause of death worldwide and has been called a hidden public health disaster.[32] Sepsis is caused by a dysregulated host response to infection,[13] which usually includes a proinflammatory phase characterized by an uncontrolled inflammatory cytokine storm, followed by a protracted anti-inflammatory phase.[33] Hypogammaglobulinemia may increase mortality from severe sepsis or septic shock compared with normal immunoglobulin levels.[34]

Many studies have investigated IVIG for the treatment of sepsis, and most studies have found that IVIG can reduce mortality in patients with sepsis. In 2012, a meta-analysis published by Soares et al[5] found that IVIG can reduce all-cause mortality in patients with sepsis according to a random-effects model (OR = 0.47; 95% CI, 0.32−0.68). A meta-analysis[6] published in Cochrane in 2013 found that IVIG significantly reduced short-term mortality in adults with sepsis based on the inclusion of all RCTs of adults with sepsis (relative risk = 0.77; 95% CI, 0.68−0.87). The last meta-analysis[35] found that IVIG reduces the mortality risk of patients with sepsis (OR = 0.50; 95% CI, 0.34−0.71). This review reevaluated the effectiveness of IVIG for the treatment of sepsis using a literature search and incorporated new primary evidence. Although the latest RCT[22] found that IVIG did not reduce mortality in patients with sepsis (the mortality rate in the control group was 12 of 17, whereas the mortality rate in the IVIG group was 12 of 16), the results of our meta-analysis found that IVIG can reduce all-cause mortality in patients with sepsis (OR = 0.61; 95% CI, 0.41−0.92; P = 0.018) (Figure 4), which is consistent with published meta-analyses.[5,6,35]

IVIG is a liquid or freeze-dried blood product generated by the combined plasma fractionation of tens of thousands of healthy donors, thus providing a broad spectrum of opsonins and IgG antibodies that bind multiple antigens and have multiple binding sites.[36] In the 1980s, IVIG was first reportedly used for the treatment of a series of sepsis animal models of streptococcal infection.[37] The results indicated that IVIG could increase the survival rate of the sepsis animals, and the mechanism may be mediated by the efficacy of phagocytosis and bacterial killing by human neutrophils.

However, the anti-inflammatory mechanisms of IVIG are complicated and remain highly controversial. IVIG treats sepsis by modulating

Table IV. Network meta-analysis comparing intravenous immunoglobulin treatment at different total doses with the control treatment: mean changes in all-cause mortality.*

Group D				
0.85 (0.21–3.38)	Group C			
0.46 (0.14–1.53)	0.54 (0.19–1.50)	Group B		
0.09 (0.00–2.99)	0.11 (0.00–3.23)	0.20 (0.01–5.68)	Group A	
0.35 (0.12–1.08)	**0.42 (0.19–0.93)**	0.77 (0.46–1.30)	3.79 (0.14–101.22)	Group P

*Comparisons should be read from left to right. Each estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Odds ratios and 95% credible intervals were calculated to estimate the all-cause mortality of each treatment. An odds ratio <1 favors the column-defining treatment. Significant results are highlighted in bold.

Group D (1.5–2 g/kg) comprised 39 patients, group C (1–1.49 g/kg) comprised 88 patients, group B (0.5–0.99 g/kg) comprised 552 patients, group A (0.45–0.49 g/kg) comprised 31 patients, and group P (control group) comprised 691 patients.

proinflammatory and anti-inflammatory processes. The mechanism of IVIG in the treatment of sepsis may include the following[38]: (1) identification and removal of pathogens and toxins,[38,39] (2) inhibition of the gene transcription of upstream mediators, (3) genes that clear and inhibit the transcription of inflammatory downstream mediators, and (4) the anti-immune apoptosis effect. In addition, based on its molecular structure, the anti-inflammatory effect of IVIG is mainly mediated by the Fc fragment,[40] but the Fab fragment can also exert anti-inflammatory effects by neutralizing autoantibodies and regulating antibody production and signaling pathways.[41] In addition, IVIG may play a role in inflammatory diseases by improving glucocorticoid receptor binding.[42]

Despite their consistent placebo-controlled study designs, all included previous RCTs used varying IVIG dosing regimens (the total dosage of IVIG ranged from 0.45 to 2 g/kg, and the treatment duration ranged from 2 to 5 days). No dose−response studies investigating IVIG for the treatment of sepsis are available, and the association between IVIG doses and sepsis treatment is not well established. We aimed to elucidate this association between different doses of IVIG and clinical

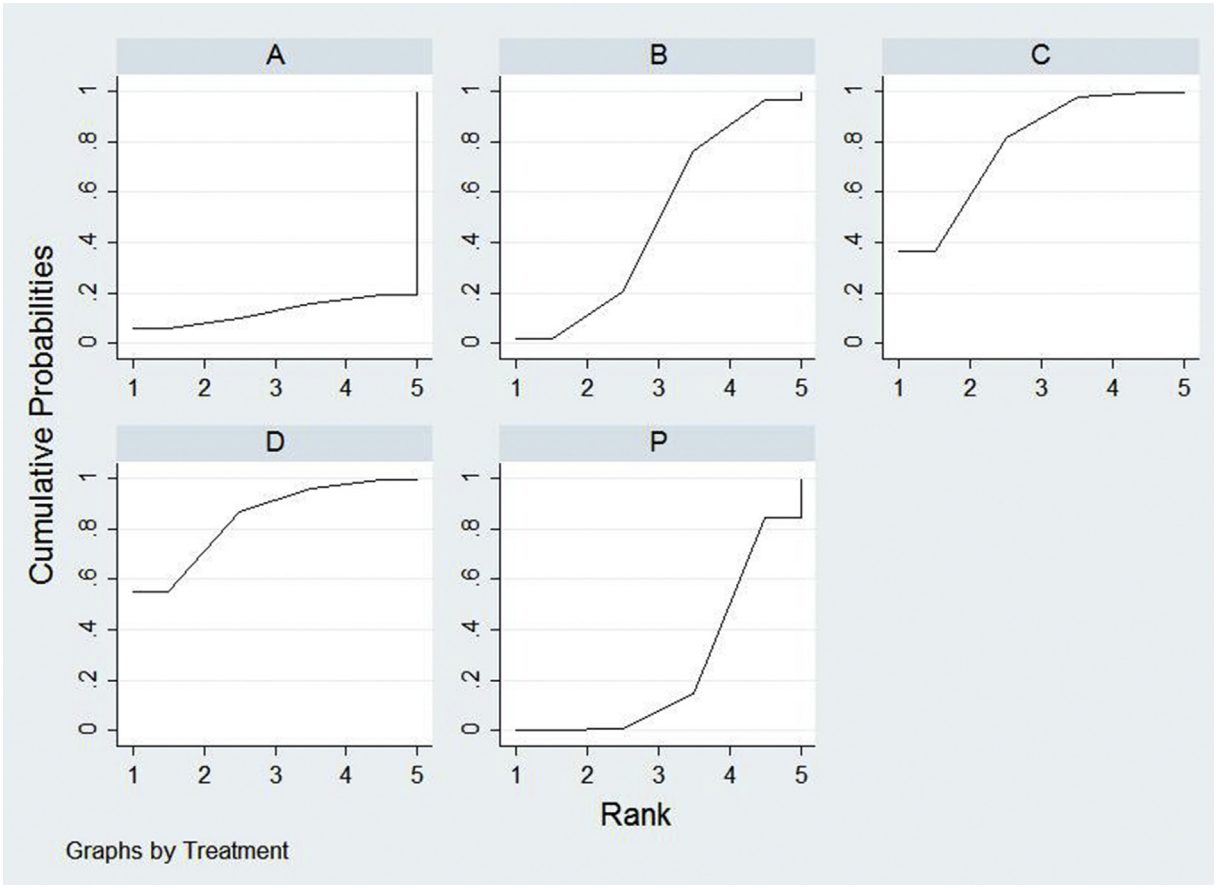

Figure 6. SUCRAs. The rank order of the interventions was as follows: Group D (SUCRA 84.7%), Group C (SUCRA 78.5%), Group B (SUCRA 48.9%), control group (SUCRA 25.1%), and Group A (SUCRA 12.8%).Group P: control group; Group A:0.45 g/kg≤total dose<0.5 g/kg; Group B: 0.5 g/kg≤total dose<1 g/kg; Group C: 1 g/kg≤total dose<1.5 g/kg; Group D:1.5 g/kg≤total dose≤2 g/kg; SUCRA:surface under the cumulative ranking curve.

outcomes (all-cause mortality) in patients with sepsis and determine the optimal dose of IVIG for the treatment of sepsis by performing a network meta-analysis.

The mean half-life of IgG ranges from 24 to 28 days in healthy humans, and the serum concentrations of IVIG after intravenous administration exhibit a rapid initial decline during 1 to 7 days, followed by a more gradual decline.[43] Regarding the characteristics of IVIG pharmacokinetic properties, our network meta-analysis applied useful and comprehensive evidence regarding the efficacy of various total doses of IVIG used for the treatment of sepsis in adults rather than the treatment duration.

By comparing the efficacy of different total doses of IVIG for the treatment of sepsis, we found that the higher dose was more effective than the lower dose (except for in group A, which was not as effective as the control group), Therefore, a dose-effect relationship likely exists within a certain range of IVIG. The SUCRA rankings (Figure 6) produced results similar to those of the network meta-analysis (Table IV). However, even with such a network meta-analysis, we were unable to detect significant differences between the different administration regimens. This review suggests that a total dose of 1.5 to 2 g/kg (Table IV) is likely the most effective for the treatment of sepsis. The results of this review

are consistent with previous results indicating that high-dose IVIG therapy is needed to achieve anti-inflammatory effects.[33] In a rat model of sepsis, the rats receiving high-dose IVIG treatment had significantly improved survival.[44] High-dose IVIG therapy may improve the serum endotoxin and HMGB1 levels and overall survival rate in sepsis by inhibiting inflammation.[45] Further studies are needed to reveal the specific mechanisms.

This network meta-analysis reveals that the lowest total dose of 0.45 to 0.5 g/kg could not decrease the all-cause mortality of sepsis (Table IV). We found that only 1 RCT[30] was included in group A. The results of this RCT indicate that the mortality rate of IVIG in the treatment of sepsis was 1 of 31, whereas that of the control group was 0 of 38. This result may be because the control group had a larger SUCRA than group A in this network meta-analysis. In addition, a large cohort study in Japan found similar results that low-dose IVIG did not decrease either intensive care unit mortality or in-hospital mortality.[46] Because of the small number of patients included in this RCT, future studies adding important evidence are needed to confirm the association between the doses of IVIG and the efficacy of sepsis treatment.

Limitations

There are some limitations to our study. First, the quality of the underlying data limit the quality of our analysis; when only RCTs with a low risk of bias were included, IVIG did not result in a significant reduction in mortality, and the sensitivity analysis is displayed in the asymmetrical funnel plot. In total, 3 of the 13 studies were judged to have a high risk of bias because of blinding. However, blinding was difficult to achieve because of the need for a clear diagnosis and drug monitoring. In total, 2 of the 13 studies did not report the loss to follow-up and patient withdrawal and were judged to have a high risk of bias because of incomplete outcome data. This high bias risk created difficulties in our intention to treat and affected the results of this meta-analysis. Second, the number of trials that assessed individual IVIG doses was small, and sufficient data are not available to perform this analysis. Third, the year of publication had an effect on the results of this meta-analysis. Six of the included studies published before 2000 reported a significant reduction in the mortality of sepsis, whereas the studies published after 2000 do not report a significant reduction in the mortality of sepsis. The effect of IVIG for the treatment of sepsis was blunted, and future studies may add important evidence regarding the associations between IVIG administration and the efficacy of sepsis treatment. Finally, the original studies did not provide the antibiotic administration time. The factors important for improving survival in patients with sepsis are the early administration of an appropriate antibiotic treatment and life support measures.[31] Therefore, antibiotic treatment could greatly influence the results of IVIG treatment. We acknowledge that this meta-analysis has certain limitations that cannot be addressed because of the inability to extract sufficient detail from pooled data. More data from large, high-quality, multicenter RCTs are required to obtain more robust results. We need more high-quality RCTs to focus on the dose and timing of IVIG treatment for sepsis to obtain more robust evidence regarding the optimal IVIG treatment concentrations.

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APPENDIX

Supplement 1. Search strategy

PubMed

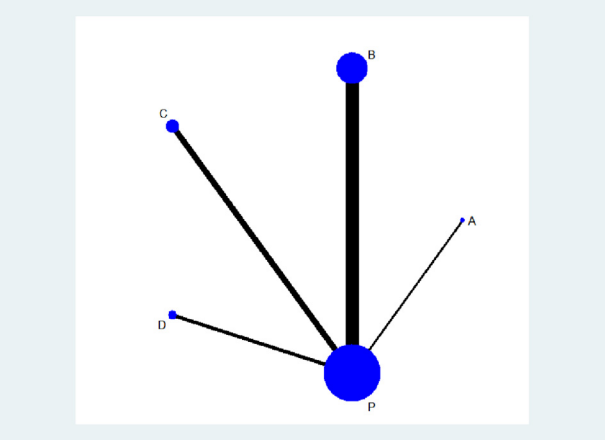
1. Immunoglobulins,Intravenous[MeSH](12007) 12313
2. Immunoglobulins[MeSH](839948) 848398
3. Intravenous immune globulin*[tw](824) 838
4. Immunoglobulin*[tw](342067) 345554
5. Ivig[tw](6417) 6579
6. 1 or 2 or 3 or 4 or 5(891548) 901079
7. Sepsis[MeSH](112984) 114849
8. Shock, septic[MeSH](21028) 21261
9. Septicemia[MeSH](112984) 114849
10. Severe sepsis[tw](7841) 7989
11. Septicem* or septicaem*[tw](21086) 21270
12. 7 or 8 or 9 or 10 or 11 (125729) 127780
13. 6 and 12(7798) 7900
14. Randomized controlled trial[pt](469648) 476704
15. Controlled clinical trial [pt](557476) 564767
16. Randomized or placebo or randomly or trial [ab] 1089384
17. 14 or 15 or 16(1226744) 1255298
18. 13 and 17(652) 661

CENTRAL

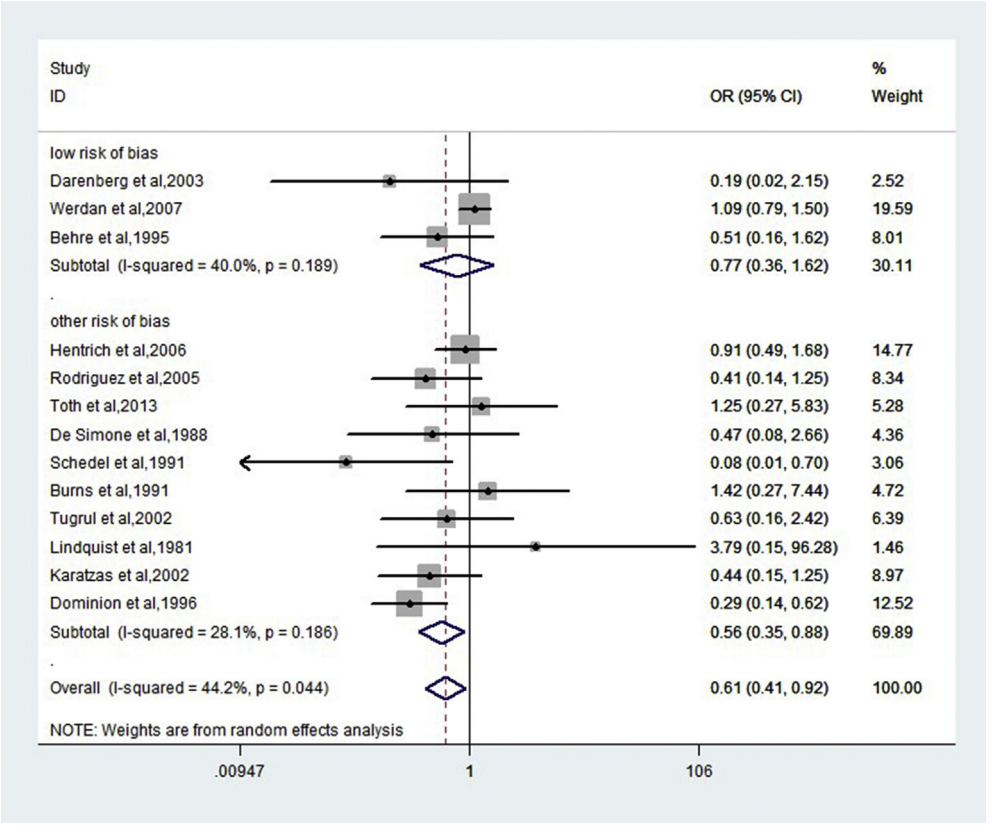
1. MeSH descriptor:[Immunoglobulins,intravenous] explode all trees 761
2. MeSH descriptor:[Immunoglobulins] explode all trees 21565
3. IVIG:ti,ab,kw 885
4. Intravenous immune globulin:ti,ab,kw 97
5. Immunoglobulin*:ti,ab,kw 12002
6. 1 or 2 or 3 or 4 or 5 26816
7. MeSH descriptor: [Sepsis] explode all trees 3924
8. MeSH descriptor: [Shock,Septic] explode all trees 749
9. Sepsis:ti,ab,kw 8034
10. Septicemia:ti,ab,kw or Septicaemia:ti,ab,kw 773
11. Septicem*:ti,ab,kw or Septicaem*:ti,ab,kw 837
12. 7 or 8 or 9 or 10 or 11 10338
13. 6 and 12 589

EMBASE

1 'Intravenous immunoglobulin'/exp 23
2 'Immunoglobulin'/exp 475031
3 'Immunoglobulin$': ti,ab,kw 183860
4 Ivig:ti,ab,kw 15193
5 #1 or #2 or #3 or #4 535782
6 'Sepsis'/exp 244342
7 'Septic shock'/exp 47860
8 'septicemia'/exp 18729
9 'severe sepsis':ti,ab,kw 13786
10 'Septicaemia':ti,ab,kw 7367
11 #6 or #7 or #8 or #9 or #10 247858
12 #5 and #11 8348
13 'Randomized controlled trial'/exp 535586
14 'Randomization'/exp 81110
15 'Double blind procedure'/exp 157693
16 'Single blind procedure'/exp 33947
17 'Random$':ti,ab,kw 289256
18 #13 or #14 or #15 or #16 or #17 911118
19 #12 and #18 295



Supplement 2. network plot

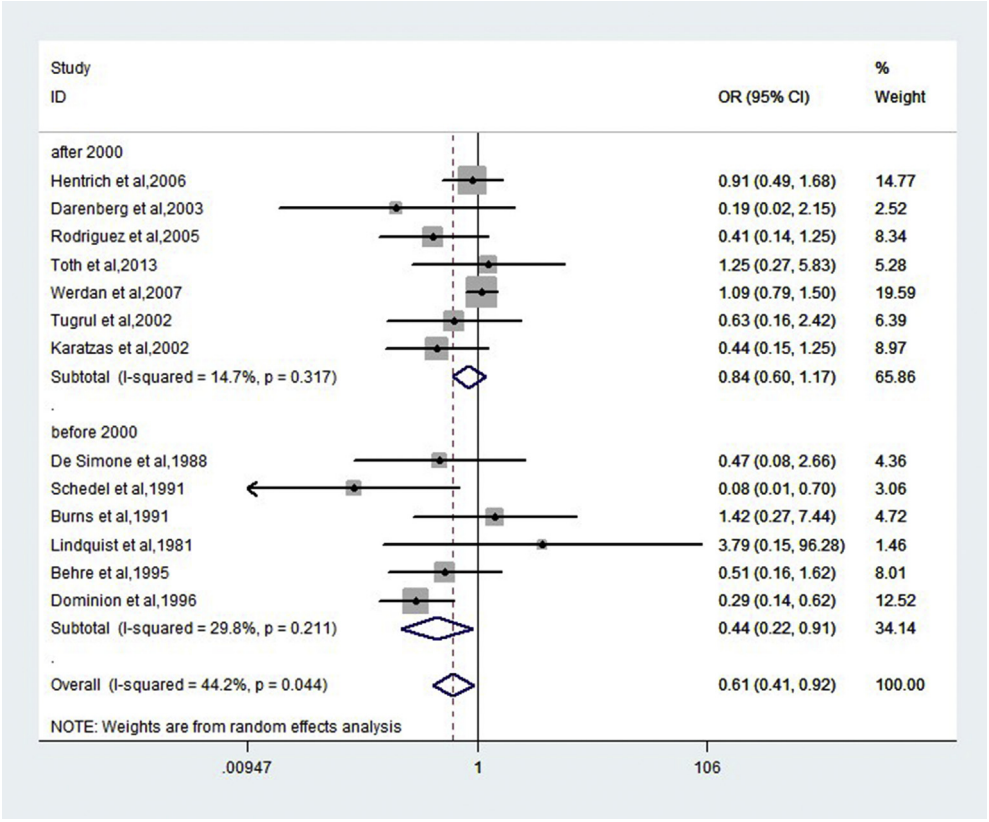


The width of lines indicates to the number of trials that assessed the comparison; the larger the size of the circle, the higher the number of patients who received the treatment.

P: control group; A: 0.45 g/kg≤total dose<0.5 g/kg; B: 0.5 g/kg≤total dose<1 g/kg; C: 1 g/kg≤total dose<1.5 g/kg; D:1.5 g/kg≤total dose≤2 g/kg.

Random-effects model to subgroup analysis based on the risk of bias of studies. When only low risk of bias of studies are included, IVIG did not show a significant reduction in mortality of sepsis (OR: 0.77; 95% CI: 0.36,1.62; p=0.485).

SUPPLEMENT 3. RESULTS OF A SUBGROUP ANALYSIS BASED ON THE RISK OF BIAS OF STUDIES



SUPPLEMENT 4. RESULTS OF A SUBGROUP ANALYSIS BASED ON THE PUBLICATION YEAR OF THE STUDIES

Random-effects model to subgroup analysis based on the publication year of the studies. When only studies published before 2000 were included, IVIG could reduce the mortality of sepsis (OR: 0.44; 95%CI: 0.22, 0.91; p=0.026), and a significant difference was observed; when only studies published after 2000 were included, IVIG could also reduce the mortality of sepsis (OR: 0.84; 95% CI: 0.60, 1.17; p=0.299), but no significant difference was observed.