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Immunoglobulin Prophylaxis in Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis

Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, and Ofer Shpilberg

From the Institute of Hematology, Davidoff Cancer Center, Infectious Diseases, Rabin Medical Center, Internal Medicine E, Beilinson Hospital, Sackler Faculty of Medicine, Tel Aviv University, Israel.

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Corresponding author: Pia Raanani, MD, Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petah-Tikva 49100, Israel; e-mail: praanani@012.net.il.

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ABSTRACT

Purpose
Because the role of immunoglobulins (IVIG) prophylaxis in patients undergoing hematopoietic stem-cell transplantation (HSCT) has not been established in terms of survival and infection prevention, we conducted a meta-analysis evaluating these issues.

Methods
Systematic review and meta-analysis of randomized-controlled trials comparing prophylaxis with polyvalent IVIG or cytomegalovirus (CMV)-IVIG and control or another preparation or dose. PUBMED, Cochrane Library, LILACS, and conference proceedings were searched. Two reviewers appraised the quality of trials and extracted data. Relative risks (RRs) with 95% CIs were estimated and pooled.

Results
Thirty trials including 4,223 patients undergoing bone marrow transplantation (BMT) were included. There was no difference in all-cause mortality when polyvalent IVIG or CMV-IVIG was compared to control (RR, 0.99; 95% CI, 0.88 to 1.12; and RR, 0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections when polyvalent IVIG was compared with control (RR, 1.00; 95% CI, 0.90 to 1.10; five trials). CMV infections were not significantly reduced with either polyvalent IVIG or CMV-IVIG. Interstitial pneumonitis was reduced with polyvalent IVIG in older studies but not in the more recent ones, nor in studies assessing CMV-IVIG. Polyvalent IVIG increased the risk for veno-occlusive disease (RR, 2.73; (95% CI, 1.11 to 6.71). Graft-versus-host disease was not affected.

Conclusion
Because there is no advantage in terms of survival or infection prevention, IVIG does not have a role in HSCT.

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INTRODUCTION

Patients undergoing hematopoietic stem-cell transplantation (HSCT; ie, bone marrow transplantation [BMT] or peripheral stem-cell transplantation [PSCT]), are highly susceptible to bacterial, fungal, and viral infections.[1-5] One approach advocated for prevention of infections is the administration of intravenous immunoglobulins (IVIG).

Favorable results of several randomized, controlled trials conducted before 2000 prompted the National Institutes of Health consensus panel to endorse the use of IVIG after allogeneic BMT.[2,5-12] Two meta-analyses in the early 1990s supported the use of IVIG in the context of BMT.[13,14] However, since then more trials have been published with one major trial showing an increased risk for veno-occlusive disease (VOD) with IVIG without a survival benefit.[15]

Because no recent meta-analysis assessed the compiled evidence available to date, we performed a systematic review and meta-analysis to examine whether the prophylactic administration of IVIG reduces mortality as well as other patient-related outcomes, including the rate of infections, hospitalization, graft-versus-host disease (GVHD), VOD and others, in patients undergoing HSCT.

METHODS

Data Sources

We searched PUBMED (January 1966 to December 2007), Central (The Cochrane Library, up to 2007, issue 1), LILACS, and the following conference proceedings published between 2002 and 2007 for recently conducted, unpublished trials in hematology and infectious diseases: Interscience Conference on Antimicrobial Agents and Chemotherapy, European Congress of Clinical Microbiology and Infectious Diseases, Annual Meeting of

Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation

Study	Intervention (type of IVIG, dose, schedule)	No. of Patients	Age (years) Mean ± SD, Median (range)	Type of Transplant (allo/auto), Type of Donor (sib/MUD)	Type of Graft
Abdel-Mageed et al[33]	Polyvalent: Gammagard, 0.25 G/kg, every week from day 8 to day +111	167	80 patients: 0-21 years; 87 patients: 22-52 years	Allo, 100%; sib, 100%	NA
	Placebo	165	85 patients: 0-21 years; 80 patients: 22-52 years		
Cordonnier et al[15]	Polyvalent: Sandoglobulin, 0.05 G/kg, every week from day 7 to day +100	53	39 (25th, 75th percentile: 30, 45)	Allo, 100%; sib, 100%	BM, 87%; PSC, 13%
	Polyvalent: Sandoglobulin, 0.25 G/kg, every week from day 7 to day +100	49	36 (25th, 75th percentile: 23, 44)		BM, 90%; PSC, 10%
	Polyvalent: Sandoglobulin, 0.5 G/kg, every week from day 7 to day +100	48	44 (25th, 75th percentile: 31, 49)		BM, 79%; PSC, 19%; CB, 2%
	Placebo	50	40 (25th, 75th percentile: 33, 34)		BM, 76%; PSC, 24%
Emanuel et al[25]	Polyvalent: Gammagard, 0.5 G/kg every 2 weeks from day 7 to day +100, then 0.25 G/kg every 2 weeks from day +100 to day +180	46	NA	Allo, 100%	BM
	Control	46			
Feinstein et al[34]	Polyvalent: Gamimune, 0.5 G/kg daily from day 6 to day 1 then 0.1 G/kg every 3rd day from day +3 to day +90	120	64 patients, 20-39 years; 56 patients, 40-60+ years	Allo, 100%; sib, 100%	BM
	Control	121	67 patients, 20-39 years; 54 patients, 40-60+ years		
Filipovich et al[3]	Polyvalent: Gamimmune, 0.5 G/kg, every other week from week 1 to week +3	10	17.6 (3-49)	Allo, 50%; auto, 50%	NA
	Polyvalent: Gammagard, 0.5 G/kg, every other week from week −1 to week +3	11	17.7 (2-42)	Allo, 55.5%; auto, 45.5%	
	Polyvalent: Sandoglobulin, 0.5 G/kg, every other week from week 1 to week +3	11	15.2 (2-50)	Allo, 55.5%; auto, 45.5%	
	Polyvalent: Immune globulin intravenous, 0.5 G/kg, every other week from week 1 to week +3	10	21.9 (1-50)	Allo, 60%; auto, 40%	
Graham-Pole et al[10]	Polyvalent: Gammagard, 0.25 G/kg, every other week from week 1 to week +3, weekly from week 1 to week +16	98	51 patients, 0-21 years; 47 patients, 21+ years	Allo, 100%	BM
	Polyvalent: Gammagard, 0.5 G/kg, every other week from week −1 to week +3, weekly from week −1 to week +16				
Lum et al[27]	Polyvalent: IVIG 0.4 G/kg, weekly from day +14 to day +79	28	NA	Allo, 100%; sib-100%	BM
	Control	26	NA		
Peltier et al[24]	Polyvalent: Gammagard 0.5 G/kg, in phase I weekly from week 1 to week +4; in phase II weekly from week 1 to week +1	Phase I, 7; phase II, 10	Phase I, 26.5 (3-43); phase II, 17.6 (3-49)	Phase I: Allo, 43%; auto, 57%; phase II: allo 50%; auto, 50%	BM
	Polyvalent: Sandoglobulin 500 mg/kg, in phase I weekly from week 1 to week +4; in phase II weekly from week 1 to week +1	Phase I, 7; phase II, 11	Phase I, 10.3 (4-18); phase II, 17.7 (2-42)	Phase I: Allo, 14%; auto, 86%; phase II: allo, 55%; auto, 45%	
	Polyvalent: Gamimmune 500 mg/kg, in phase I weekly from week 1 to week +4; in phase II weekly from week 1 to week +1	Phase I, 7; phase II, 11	Phase I, 16.9 (3-26); phase II, 15.2 (2-50)	Phase I: Allo, 43%; auto, 57%; phase II: allo, 55%; auto, 45%	
Poynton et al[4]	Polyvalent: IgM and IgA enriched IVIG (pentaglobin) 0.35 G/k, days 0, +3, +7, then weekly until neutrophils $> 0.5 \times 10^9$/L	29	37 (15-64)	Allo, 48%; auto, 52%	BM
	Control	34	33 (15-59)	Allo, 47%; auto, 53%	
Raiola et al[37]	Polyvalent: Pentaglobulin 0.2 G/kg, every 2 weeks from day 7 to day +100	89	34	Allo, 100%	BM
	Polyvalent: Sandoglobulin 0.4 G/kg, every 2 weeks from day 7 to day +100				
Sullivan et al[2]	Polyvalent: Gamimune N 0.5 G/kg, weekly from day 7 to day +90	191	58 patients, < 20 years; 133 patients, ≥ 20 years	Allo, 87%; auto, 11%	BM
	Control	191	66 patients, < 20 years; 125 patients, ≥ 20 years	Allo, 87%; auto, 10%	

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Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation (continued)

Study	Hematologic Malignancies	GVHD Prophylaxis	Infection Prophylaxis (bacterial, fungal viral, PCP, CMV)	Outcomes Reported by ITT	Allocation Generation, Concealment	Blinding
Abdel-Mageed et al[33]	AL, 58%; CML, 26% AL, 55%; CML, 26%	NA	Nonabsorbable antibiotics, fluconazole, acyclovir	No (18 excluded)	B, B	None
Cordonnier et al[15]	AL, 51%; CML, 32% AL, 55%; CML, 26% AL, 48%; CML, 32% AL, 40%; CML, 34%	MTX and /or CsA	Nonabsorbable antibiotics, oral polyenes, acyclovir	Yes	A, A	DB
Emanuel et al[25]	NA NA	NA	NA	Yes	B, B	None
Feinstein et al[34]	NA NA	MTX and/or CsA and/or steroids	Ceftazidime, fluconazole, acyclovir, TMP-SMX, gancyclovir	No (19 excluded)	B, B	None
Filipovich et al[3]	AL, 50%; CML, 30% AL, 45.5%; CML, 27% AL, 27%; CML, 27% AL, 30%; CML, 50%	NA	NA	Yes	B, A	DB
Graham-Pole et al[10]	AL, 55%; CML, 23%	NA	NA	No (57 excluded)	B, B	None
Lum et al[27]	NA	CsA and steroids	NA	Yes	B, B	None
Peltier et al[24]	Phase I: AL, 43%; CML, 43%; phase II: AL, 50%; CML, 30% Phase I: AL, 86%; CML, 0%; phase II: AL, 45%; CML, 27% Phase I: AL, 71%; CML, 14%; phase II: AL, 27%; CML, 27%	NA	NA	NA	B, B	DB
Poynton et al[4]	AL, 34%; CML, 17% AL, 50%; CML, 6%	CsA	Nonabsorbable antibiotics or ciprofloxacin	No (9 excluded)	B, B	None
Raiola et al[37]	AL, 39%; CML, 47%	NA	NA	Yes	B, B	NA
Sullivan et al[2]	AL, 42%; CML, 24% AL, 57%; CML, 17%	MTX and /or CsA and/or steroids	Enteric decontamination, TMP-SMX, acyclovir	No (14 excluded)	B, B	None

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Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation (continued)

Study	Intervention (type of IVIG, dose, schedule)	No. of Patients	Age (years) Mean ± SD, Median (range)	Type of Transplant (allo/auto), Type of Donor (sib/MUD)	Type of Graft
Sullivan et al[35]	Polyvalent: Gammagard 0.5 G/kg, days 7, −1 then weekly from day +6 to day +90	249	NA	Allo, 100%; MUD, 100%	BM
	Placebo	248			
Ustun et al[31]	Polyvalent: IVIG 0.5 G/kg, day −4 then weekly until neutrophils $> 0.5 \times 10^9$/L	7	NA	Allo, 100%; sib, 100%	PSC
	Control	7			
Winston et al[1]	Polyvalent: Cohn fraction II gamma globulin 20 mL/kg, before initiation of conditioning and then once weekly until day +120	18	19 (6-48)	Allo, 100%; sib, 100%	BM
	Control	18	20 (4-34)		
Winston et al[9]	Polyvalent: Cohn fraction II gamma globulin 20 mL/kg, before initiation of conditioning and then once weekly until day +120	38	19 (6-48)	Allo, 100%; sib, 100%	BM
	Control	37	20 (4-45)		
Winston et al[26]	Polyvalent: Sandoglobulin 1 G/kg, before initiation of conditioning and then once weekly until day +120	27	33 (9-44)	Allo, 100%; sib, 63%; MUD, 37%	BM
	Control	24	30 (5-45)	Allo, 100%; sib, 66.6%; MUD, 33.3%	
Winston et al[12]	Polyvalent: Venoglobulin 0.1 G/kg, day 2, then weekly from day 0 to day +90, then monthly from day +90 to day +360	206	32 (5-58)	Allo, 100%; sib, 73%; MUD, 27%	BM
	Polyvalent: Venoglobulin 0.25 G/kg, day 2, then weekly from day 0 to day +90, then monthly from day +90 to day +360	208	33 (5-61)	Allo, 100%; sib, 76%; MUD, 24%	
	Polyvalent: Venoglobulin 0.5 G/kg, day 2, then weekly from day 0 to day +90, then monthly from day +90 to day +360	204	33 (5-57)	Allo, 100%; sib, 76%; MUD, 24%	
Wolff et al[28]	Polyvalent: Sandoglobulin 0.5 G/kg, weekly, from start of chemotherapy until severe side effects or neutropenia resolution	82	38 (17-71)	Auto, 76% myelosuppressive therapy, 24%	BM
	Control	88	42 (17-64)	Auto, 72% myelosuppressive therapy, 28%	
Boeckh et al[36]	Hyperimmune: anti CMV specific monoclonal ab (MSL, 109) 60 mg/kg, every 14 days from day 1 to day +84	59	41	Allo, 100%; sib, 71%; MUD, 29%	PSC
	Hyperimmune: anti CMV specific monoclonal ab (MSL, 109) 15 mg/kg, every 14 days from day 1 to day +84	60	38	Allo, 100%; sib, 72%; MUD, 28%	
	Placebo	60	38	Allo, 100%; sib,65%; MUD-35%	
Bowden et al[7]	Hyperimmune: CMV IVIG 150 mg/kg + seronegative blood products, days 5, −1, +6, +20, +34, dose of 150 mg/kg; days +48; +62, dose of 100 mg/kg	23	21 (1-58)	Allo, 100%	BM
	Seronegative blood products alone (control)	28	24 (6-44)		
	Hyperimmune: CMV IVIG 150 mg/kg, days 5, −1, +6, +20, +34, dose of 150 mg/kg; days +48; +62, dose of 100 mg/kg	22	22 (3-41)		
	Control	24	27 (7-41)		
Bowden et al[23]	Hyperimmune: CMV IVIG 200 mg/kg, days 8; −6; +1; +7; +14; +21; +28; +42; +56; +70	61	30 (2-56)	Allo, 100%	BM
	Control	62	27 (2-48)		
Bordigoni et al[22]	Hyperimmune: anti CMV IgG enriched plasma 4 mL/kg, days: −7; −3; 0; +15; +30; 45; +60; +75; +90	30	14 ± 11	Allo, 62%; auto, 32%	BM
	Control	30	8 ± 7		

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Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation (continued)

Study	Hematologic Malignancies	GVHD Prophylaxis	Infection Prophylaxis (bacterial, fungal viral, PCP, CMV)	Outcomes Reported by ITT	Allocation Generation, Concealment	Blinding
Sullivan et al[35]	NA	MTX and/or CsA	NA	Yes	B, B	DB
Ustun et al[31]	AL, 14%; CML, 28%	MTX and CsA	NA	Yes	B, B	NA
Winston et al[1]	AL, 78% AL, 83%	MTX	TMP-SMX	No (5 excluded)	B, B	None
Winston et al[9]	AL, 79% AL, 78%	MTX and/or CsA and/or T cell depletion	TMP-SMX	No (14 excluded)	B, B	None
Winston et al[26]	AL, 41%; CML, 48% AL, 46%; CML, 21%	MTX and/or CsA and/or steroids and/or T cell depletion and/or immunotoxin	Nonabsorbable vancomycin or polymixin or norfloxacin	Yes	B, B	None
Winston et al[12]	AL, 42%; CML, 35% AL, 41%; CML, 34% AL, 36%; CML, 34%	MTX and/or CsA and/or steroids	Quinolones and nystatin and acyclovir and gancyclovir, TMP-SMX	No (9 excluded)	B, B	DB
Wolff et al[28]	NA	NA	Oral antibiotics, acyclovir	Yes	A, B	None
Boeckh et al[36]	NA	NA	NA	Yes	A, A	DB
Bowden et al[7]	AL, 57%; CML, 35% AL, 39%; CML, 39% AL, 50%; CML, 45% AL, 50%; CML, 42%	MTX and/or CsA	NA	No (2 excluded)	A, A	None
Bowden et al[23]	AL, 34%; CML, 38% AL, 45%; CML, 31%	MTX and/or CsA and/or other	NA	No (3 excluded)	A, B	None
Bordigoni et al[22]	AL, 65%; CML, 5%	MTX and/or CsA and/or T cell depletion	Acyclovir	Yes	A, A	None

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Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation (continued)

Study	Intervention (type of IVIG, dose, schedule)	No. of Patients	Age (years) Mean ± SD, Median (range)	Type of Transplant (allo/auto), Type of Donor (sib/MUD)	Type of Graft
Condie et al[6]	Hyperimmune: CMV IVIG; 200 mg/kg, days; post-transplant: +25; +50; +75	17	13 ± 7	Allo, 100%	BM
	CMV deficient IVIG; 200 mg/kg, days; post-transplant: +25; +50; +75	18	12 ± 8		
	Control	20	17 ± 6		
Jacobsen et al[20]	Hyperimmune: CMV IVIG; 0.1 G protein/kg, days 7, +13, +33, +53, +79, +93	26	22 (7-43)	Allo, 100%	BM
	Control IVIG 0.1 G protein/kg, days 7, +13, +33, +53, +79, +93	23	23 (11-38)		
Meyers et al[19]	Hyperimmune: anti-CMV globulin 6 mL/m^2, days 4, −2, then weekly to day 77	30	20 (3-40)	Allo, 100%	BM
	Control	32	24 (5-43)		
Ringden et al[21]	Hyperimmune: CMV plasma 200 mg/kg, days post-transplant: +3, +4, +25, +26, +50, +51, +75, +76	27	24 (1-41)	Allo, 100%	BM
	Control	27	30 (1-49)		
Ruutu et al[29]	Hyperimmune: anti-CMV globulin 0.4 G/kg on day 8, then 0.2 G/kg; weekly from day 8 to day +42, then bi-weekly to day +70	13	26 (9-55)	Allo, 100%; sib, 85%; MUD, 15%	BM
	Control	15	33 (2-51)	Allo, 100%; sib, 94%; MUD, 6%	
Serrano et al[32]	Hyperimmune: CMV IVIG 0.15 G/kg, every 2 weeks from day +2 to day +86, then monthly till day +360	49	29.7 (6-59)	Allo, 100%; sib, 100%	BM
	Control	43	26.8 (4-50)		
Winston et al[18]	Hyperimmune: anti-CMV plasma 10mL/kg before conditioning, then every 15 days from on day +3 to day +120	24	20 (4-46)	Allo, 100%; sib, 100%	BM
	Control	24	13 (8-48)		
Zikos et al[30]	Hyperimmune: anti-CMV globulin 0.1 G/kg weekly from day 7 to day +100 days	64	36 (11-56)	Allo, 100%; sib, 100%	BM, 81%; PSC, 19%
	Polyvalent: Sandoglobulin, 0.4 G/kg, weekly from day 7 to day +100 days	64	33.5 (17-55)		BM, 66%; PSC, 34%

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the American Society of Hematology and the annual Meeting of the European Hematology Association. The terms "immunoglobulins" or "gammaglobulins" or specific gammaglobulins and similar and the terms "hematologic neoplasms" or "hematologic malignancies" or "transplant" or "autotransplant" or "allotransplant" or "bone marrow transplant" or "peripheral stem-cell transplant" and similar were selected. We scanned references of all included trials and reviews identified for additional trials that did not come up in our search.

Study Selection

We included all randomized, controlled trials comparing the administration of intravenous or intramuscular polyvalent immunoglobulins (polyvalent IVIG) or hyperimmune cytomegalovirus-IVIG (CMV-IVIG) preparations with placebo, no treatment or another immunoglobulin preparation, a different administration schedule or dose for HSCT recipients. We included trials regardless of publication status, date of publication, and language. One author (P.R.) screened all references identified through our search strategy; two reviewers independently inspected each abstract and applied inclusion criteria. For possibly relevant articles or in the event of disagreement between the two reviewers, we obtained and independently inspected the full article.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from included trials. In the event of disagreement between the two reviewers, a third reviewer extracted the data and results were attained by consensus. We contacted the authors of trials for missing data when necessary. We assessed allocation concealment, allocation generation, blinding, and intention-to-treat (ITT) analysis. We graded allocation concealment and generation as adequate, unclear, inadequate or not used using the criteria specified in the Cochrane handbook.[16] We used an individual component approach for quality assessment, since the use of composite scales has yielded conflicting results.[17]

Definition of Outcomes and Comparisons

The primary outcomes were all-cause mortality and clinically documented infections. Secondary outcomes included microbiologically documented bacterial infections, CMV infection, interstitial pneumonitis, acute GVHD, VOD, and adverse events. Mortality was extracted at 100 to 200 days and 1 to 2 years after HSCT.

We conducted the following comparisons: polyvalent IVIG versus placebo or no treatment; CMV- IVIG versus placebo or no treatment; polyvalent IVIG or CMV-IVIG versus placebo or no treatment; polyvalent IVIG versus CMV-IVIG; polyvalent IVIG at a dose of 250 mg/kg versus polyvalent IVIG at a dose of 500 mg/kg.

Data Synthesis and Analysis

For each trial, results were expressed as relative risks (RRs) with 95% CIs for dichotomous data (Review Manager [RevMan], version 4.2 for Windows; the Cochrane Collaboration, Oxford, United Kingdom). We conducted meta-analysis using a fixed-effect model. Outcomes were extracted preferentially by ITT analysis, including all individuals randomly assigned in the outcome assessment. However, when this was impossible, data were extracted per-protocol analyses.

Table 1. Included Trials: Bone Marrow/Peripheral Stem Cell Transplantation (continued)

Study	Hematologic Malignancies	GVHD Prophylaxis	Infection Prophylaxis (bacterial, fungal viral, PCP, CMV)	Outcomes Reported by ITT	Allocation Generation, Concealment	Blinding
Condie et al[6]	AL, 100%	MTX	NA	Yes	B, B	None
Jacobsen et al[20]	AL, 59%; CML, 31% AL, 83%; CML, 13%	MTX or CsA	NA	Yes	B, B	None
Meyers et al[19]	AL, 80%; CML, 20% AL, 69%; CML, 31%	MTX	NA	No (6 excluded)	B, B	None
Ringden et al[21]	AL, 81%; CML, 29% AL, 63%; CML, 30%	CsA and/or MTX	NA	Yes	B, B	None
Ruutu et al[29]	AL, 54%; CML, 38% AL, 40%; CML, 26%	MTX and/or CsA and/or steroids	Acyclovir	Yes	B, B	None
Serrano et al[32]	AL, 49%; CML, 26% AL, 56%; CML, 19%	MTX and/or CsA and/or T cell depletion	Nystatin, ciprofloxacin, fluconazole, acyclovir, TMP-SMX	Yes	B, B	None
Winston et al[18]	AL, 54% AL, 50%	MTX	Nonabsorbable antibiotics, TMP-SMX	No (6 excluded)	B, B	None
Zikos et al[30]	AL, 45%; CML, 28% AL, 53%; CML, 25%	CsA and/or MTX	Acyclovir, TMP-SMX	Yes	B, B	None

Abbreviations: allo, allogeneic; auto, autologous; sib, sibling; MUD, matched unrelated donor; ITT, intention to treat; allocation generation, concealment: A, adequate; B, unclear; MUD, matched unrelated donor; GVHD, graft-versus-host disease; AL, acute leukemia; NA, not available; CML, chronic myeloid leukemia; BM, bone marrow; PSC, peripheral stem cells; DB, double blind; MTX, methotrexate; CsA, cyclosporine A; TMP-SMX, trimethoprim-sulfamethoxazole.

We assessed for heterogeneity in the results of the trials using a χ^2 test of heterogeneity ($P < .1$) and the I^2 measure of inconsistency. Subgroup analyses were conducted for type of transplantation (autologous *v* allogeneic) and the use of antifungal prophylaxis. We could not conduct separate subgroup analyses for type of graft (BMT *v* peripheral blood stem cell transplantation).

We searched for reasons for heterogeneity assessing the dose of IVIG used and type of HSCT (allogeneic or autologous). We performed sensitivity analyses to assess the effect of individual methodologic quality measures on effect estimates, including allocation generation, concealment, and blinding.

RESULTS

The computerized search strategy identified 855 trials, not all relevant for this review. Seventy-three trials were considered for this review, including eight abstracts from conference proceedings. Forty-three trials were excluded, including five reports identified as duplicate publications and considered under their primary reference (Fig 1). Thirty trials performed between 1982 and 2003 and reporting on patients receiving IVIG after BMT (26 trials) or PSCT (two trials) or both (two trials) fulfilled inclusion criteria (Table 1).[1-4, 6, 7, 9, 10, 12, 15, 18-37]

Prophylaxis was initiated in most trials during conditioning (26 trials) or immediately after transplant (four trials) and was administered either weekly (16 trials), bi-weekly (eight trials), or by using a different schedule (six trials). In most trials prophylaxis was given for 3 months and the maximal period of administration was 1 year (Table 1).

Polyvalent IVIG Versus Placebo or No Intervention (control)

Primary outcomes. Eight trials reported all-cause mortality, four reported at 100 to 200 days[15,31,35,38] and four reported at 2 years and more.[2,4,5,27] There was no difference in the risk for all-cause mortality between polyvalent IVIG and control (RR, 0.99; 95% CI, 0.88 to 1.12), with no significant heterogeneity ($P = .4$; $I^2 = 3.3\%$; Fig 2).[2,4,15,18,21-23,26,27,31,35,38]

Analysis according to transplant type did not yield a difference in mortality between polyvalent IVIG and control, neither for the allogeneic transplant only group (RR, 1.07; 95% CI, 0.79 to 1.44) nor for the combined allogeneic and autologous transplant group (RR, 0.95; 95% CI, 0.81 to 1.10). In three trials that reported no antifungal prophylaxis the RR for mortality with IVIG was 0.88 (95% CI, 0.76 to 1.02), while

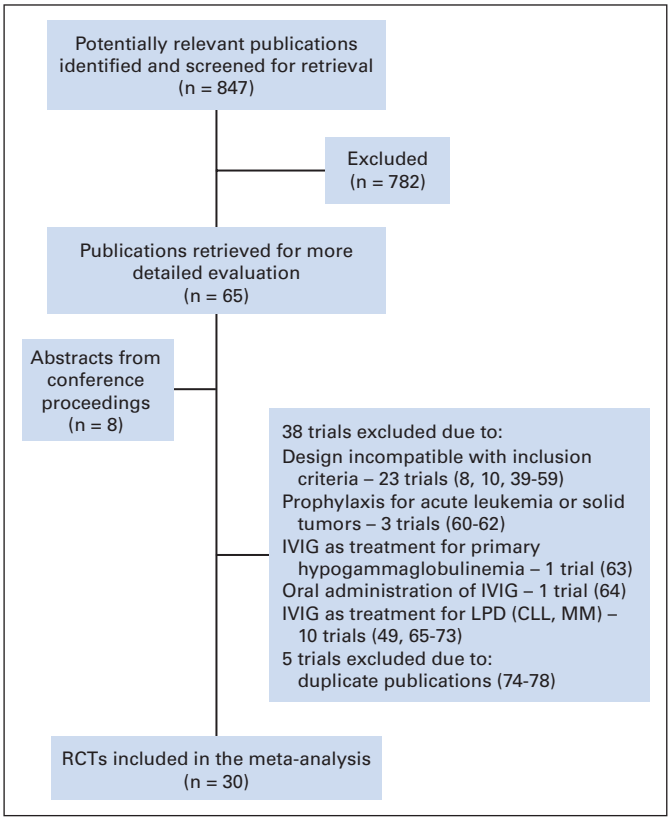

Fig 1. Publications identified for study and exclusions. RCT, randomized controlled trial; LPD, lymphoproliferative disorders; CLL, chronic lymphocytic leukemia; MM, multiple myeloma.

in trials using antifungal prophylaxis the RR was 1.07 (95% CI, 0.74 to 1.53).

There was no difference in all-cause mortality according to sensitivity analyses by randomization generation or blinding (Appendix Fig A1 online only): RR of 1.40 (95% CI, 0.88 to 2.22) for trials with adequate randomization generation and RR of 0.93 (95% CI, 0.83 to 1.05) for trials in which randomization generation was not clear; RR of 0.94 (95% CI, 0.76 to 1.17) for trials which were blinded and RR of 0.99 (95% CI, 0.86 to 1.14) for those not blinded. Six trials reported results by ITT (RR, 1.04; 95% CI, 0.87 to 1.24), while three analyzed available cases only (RR, 0.91; 95% CI, 0.79 to 1.06).

Polyvalent IVIG administration did not result in a decrease in the occurrence of clinically documented infections (RR, 1.00; 95% CI, 0.90 to 1.10; five trials). There was no evidence for heterogeneity in these comparisons ($P = .97$; $I^2 = 0\%$; Fig 3).[4,15,31,34,38] There was no difference in clinically documented infections between trials of adequate randomization generation (RR, 0.99; 95% CI, 0.86 to 1.14) and those in which randomization generation was not clear (RR, 1.00; 95% CI, 0.86 to 1.17). There was no difference in clinically documented infections between trials which were blinded (RR, 1.01; 95% CI, 0.91 to 1.12) and those not blinded (RR, 0.99; 95% CI, 0.86 to 1.15).

Secondary outcomes. Polyvalent IVIG did not significantly alter the occurrence of CMV infections when analyzed per patient (RR, 0.84; 95% CI, 0.66 to 1.07; six trials; Fig 4[1,2,4,9,15,25,26,31,34,38]) or as episode per patient month (RR, 0.70; 95% CI, 0.49 to 1.02). Polyvalent IVIG significantly reduced the risk for developing interstitial pneumonitis (RR, 0.64; 95% CI, 0.45 to 0.89; seven trials, 990 patients; Fig 4).

Polyvalent IVIG administration compared with control did not result in a decrease in the risk for microbiologically documented bacterial infections, when analyzed per patient (RR, 1.00; 95% CI, 0.88 to 1.15; seven trials, 1,186 patients), or as episodes per patient-month (RR, 0.97; 95% CI, 0.82 to 1.16; six trials, 3,542 patient-months). The risk of infection-related death was not affected significantly (RR, 0.64; 95% CI, 0.28 to 1.49, three trials).

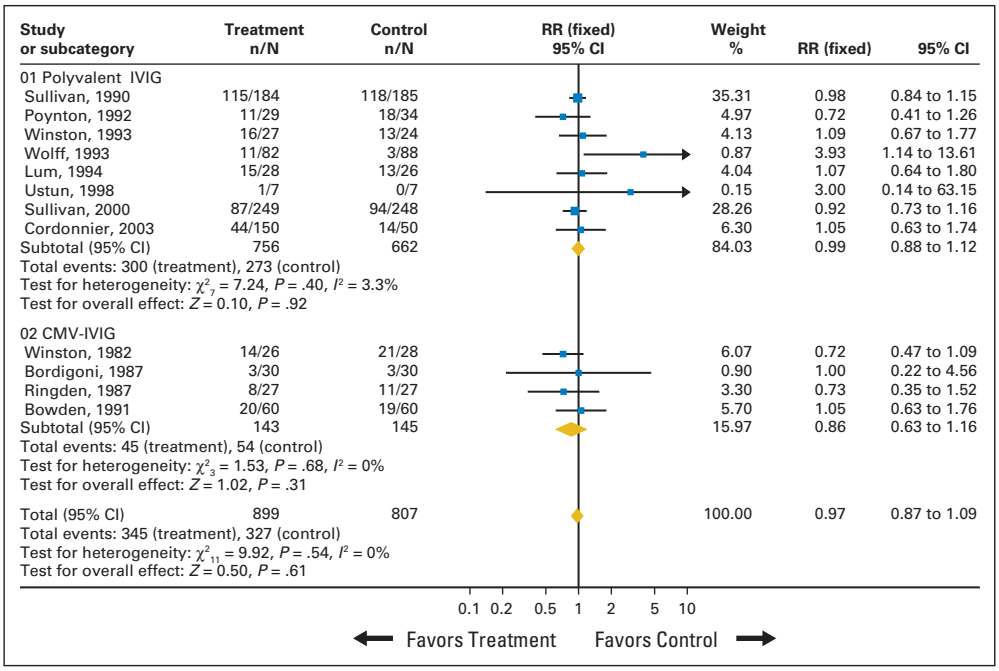

Fig 2. All-cause mortality at end of follow-up in trials comparing polyvalent immunoglobulins (IVIG) versus placebo or no treatment and hyperimmune CMV (cytomegalovirus)-IVIG versus placebo or no treatment.[2,4,15,18,21-23,26,27,31,35,38]

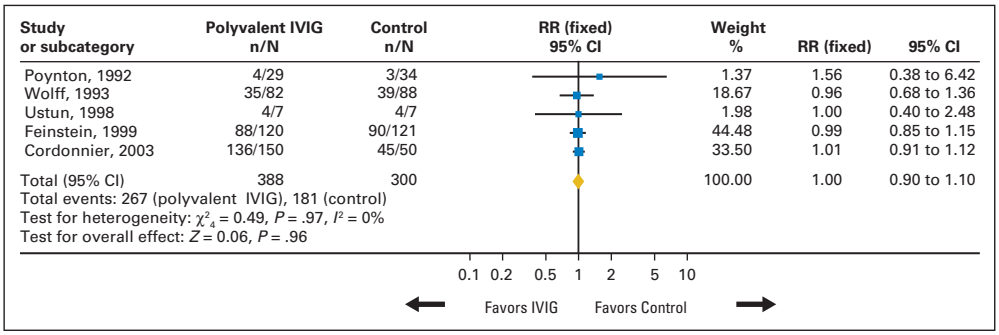

Fig 3. Clinically documented infections in trials comparing polyvalent immunoglobulins (IVIG) versus placebo or no treatment.[4,15,31,34,38] RR, relative risk.

When compared with control, polyvalent IVIG prophylaxis did not result in a decrease in the risk of acute GVHD (RR, 0.93; 95% CI, 0.83 to 1.04, seven trials), but resulted in a significantly increased risk for developing VOD (RR, 2.73; 95% CI, 1.11 to 6.71, four trials; Fig 4).

When we separated the trials according to the type of transplant, there was an increased risk for VOD in both the allogeneic only group, RR 2.04 (95% CI 0.76-5.49, three trials) and the autologous only group (RR, 11.8; 95% CI, 0.66 to 210.03; one trial).

There was a significant increase in adverse effects in the polyvalent IVIG arm compared with control (RR, 8.12; 95% CI, 3.15 to 20.97; five trials). Adverse effects did not require discontinuation of treatment. They included mainly early adverse effects: fever, chills, nausea and vomiting, headache, myalgia, rash, and hypotension without anaphylaxis.

CMV-IVIG Versus Placebo or No Intervention (control)

Primary outcome. There was no difference in the risk for all-cause mortality (RR, 0.86; 95% CI, 0.63 to 1.16; four trials; Fig 2), with no statistical evidence of heterogeneity ($P = .68$; $I^2 = 0\%$). Mortality was assessed in these trials between 62 days[7] and 3 years after randomization.[18,21]

When we combined the 12 trials assessing all-cause mortality with either polyvalent IVIG or CMV-IVIG as compared with control (Fig 2), there was no difference in the risk for all-cause mortality (RR, 0.97; 95% CI, 0.87 to 1.09) and no statistical evidence of heterogeneity ($P = .54$,; $I^2 = 0\%$).

Secondary outcomes. Eight trials reported CMV infections and five trials reported interstitial pneumonitis. CMV-IVIG prophylaxis did not result in a decrease in the occurrence of CMV infections (RR, 1.02; 95% CI, 0.82 to 1.26, eight trials), with statistical evidence of heterogeneity ($P = .04$; $I^2 = 53\%$) or interstitial pneumonitis (RR, 0.95; 95% CI, 0.58 to 1.56; five trials), with no statistical evidence of heterogeneity ($P = .27$; $I^2 = 22.7\%$).

CMV-IVIG administration did not result in a statistically significant decrease in the risk of infection-related death (RR, 0.67; 95% CI, 0.34 to 1.32; three trials), with no statistical evidence of heterogeneity

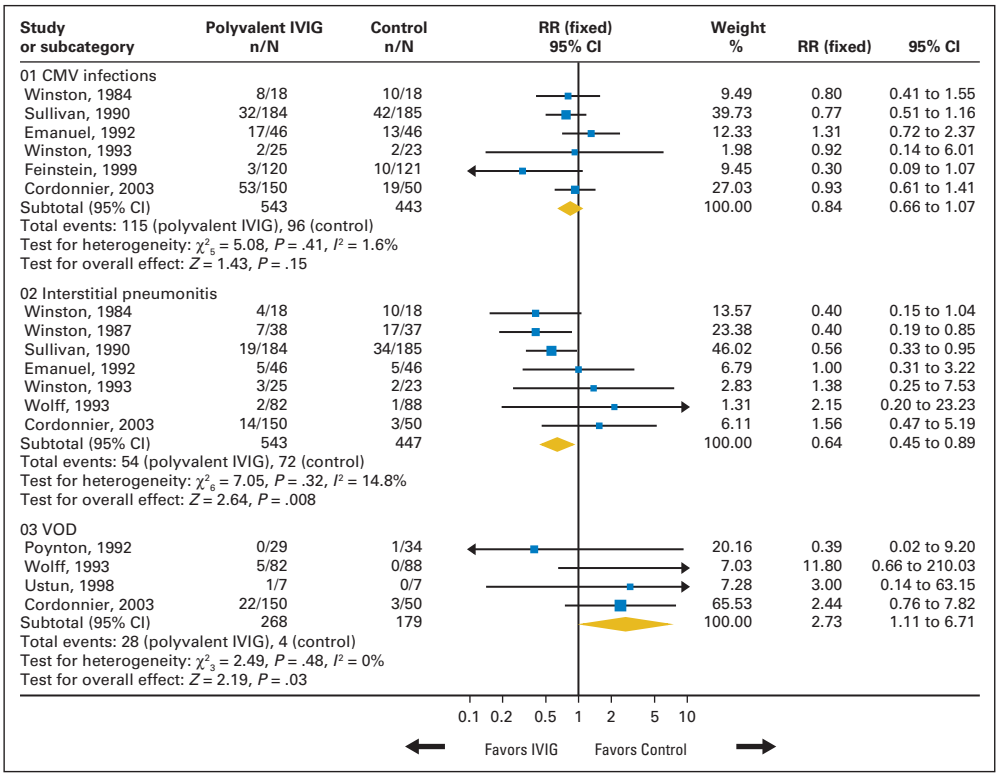

Fig 4. Cytomegalovirus (CMV) infections, interstitial pneumonitis, and veno-occlusive disease (VOD) in trials comparing polyvalent immunoglobulins (IVIG) versus placebo or no treatment.[1,2,4,9,15,25,26,31,34,38] RR, relative risk.

Table 2. Comparison Between Various Meta-Analyses of Prophylaxis IVIG in BMT Patients

Study	No. of Studies	Type of Participants	Clinical Outcome			
			All Cause Mortality	CMV Infection	Interstitial Pneumonia	Acute GVHD
Bass et al[13]	12	BMT recipients	Significantly reduced by IVIG	Not significantly reduced by IVIG	Significantly reduced by IVIG	Not significantly reduced by IVIG
Glowaki et al[14]	18	BMT recipients and solid organ recipients	Not significantly reduced by IVIG	Significantly reduced by IVIG	NA	NA
Raanani et al (this study)	30	BMT	Not significantly reduced by IVIG	Not significantly reduced by IVIG	Significantly reduced by IVIG	Not significantly reduced by IVIG

Abbreviations: BMT, bone marrow transplantation; CMV, cytomegalovirus; GVHD, graft-versus-host disease; IVIG, immunoglobulin; NA, not available.

($P = .67$; $I^2 = 0\%$) and acute GVHD compared with control (RR, 1.02; 95% CI, 0.72 to 1.44; five trials) with no statistical evidence of heterogeneity ($P = .88$; $I^2 = 0\%$).

Only one trial reported adverse effects for CMV-IVIG as compared with control with adverse effects occurring in the CMV-IVIG arm only (3 *v* none of 27 patients in each arm).[21]

Polyvalent IVIG Versus CMV-IVIG

When we compared polyvalent IVIG and CMV-IVIG, we found that all-cause mortality was higher with polyvalent IVIG without statistical significance (RR, 1.46; 95% CI, 0.92 to 2.32; three trials) with no significant heterogeneity ($P = .99$; $I^2 = 0\%$). The risk for CMV infection, but not for interstitial pneumonitis, was higher with polyvalent IVIG prophylaxis than with CMV-IVIG prophylaxis (RR, 1.42; 95% CI, 1.07 to 1.89; three trials; *v* RR, 0.83; 95% CI, 0.40 to 1.75; two trials, respectively).

There was a higher rate of acute GVHD with polyvalent IVIG at a dose of 250 mg/kg as compared with 500 mg/kg (RR, 1.32; 95% CI, 1.13 to 1.55; three trials).

DISCUSSION

Our review shows that IVIG prophylaxis in patients undergoing HSCT, does not affect mortality or infection-related outcomes. It decreases the rate of interstitial pneumonitis and increases the risk for VOD.

Two meta-analyses have previously addressed IVIG treatment for patients undergoing BMT (Table 2).[13,14] Ours is the largest meta-analysis published so far and it supports the Glowaki et al conclusions regarding lack of effect on all cause mortality as well as the Bass et al conclusions regarding the other outcomes such as CMV infection, interstitial pneumonitis, and acute GVHD prophylaxis.

IVIG prophylaxis did not affect our primary outcome which was all cause mortality. This might be due to its lack of effect on clinically documented infections and acute GVHD, the major causes of early death in patients undergoing allogeneic HSCT. Furthermore, the beneficial effect of IVIG on interstitial pneumonitis was outweighed by its deleterious influence on VOD.

IVIG did not influence also our second primary outcome (ie, clinically documented infections). This might be due to the fact that causes for infections in patients who receive transplantation are multifactorial and consist also of causes other than hypogammaglobulinemia.

The most significant beneficial outcome in our study was the reduction of 36% in the occurrence of interstitial pneumonitis by polyvalent IVIG. Of note, our results favored treatment with IVIG only in the studies conducted, in the 1980s while the later studies, employing contemporary diagnostic and prophylactic strategies for CMV infections, actually favored control over IVIG (Fig 4). Our data did not allow us to separate between CMV and non-CMV interstitial pneumonitis. Because both outcomes probably measure the same disease, the truer effect estimate for current practice is probably that of the newer studies.

An interesting finding in our meta-analysis was that polyvalent IVIG prophylaxis resulted in a significantly increased risk for developing hepatic VOD. Several possibilities might explain this disturbing increased risk. One explanation is an immunological insult to liver cells by IVIG which contain high levels of antibodies similar to the antibody gemtuzumab ozogamicin, which causes VOD through receptor mediated targeting of CD33 cells in the liver. Another mechanism suggested is through induction of hyperviscosity affecting the circulation in the small hepatic venules by IVIG. Alternatively, the effects of cytokines triggered by IVIG administration might also contribute to the development of VOD.[15]

Therefore, our findings do not support the National Institutes of Health consensus recommendations for patients after BMT/HSCT.[11] The compiled data available to date from randomized controlled trials does not demonstrate an improvement in mortality or morbidity with IVIG.

The main limitation of this review is that the majority of studies were old, with many of them reporting on patients treated in the 1980s and 1990s. In most studies, donors were HLA-matched siblings while the growing number of matched unrelated, haploidentical and cord blood transplants as well as the newer techniques of reduced intensity conditioning are not reflected in them.

In conclusion, lack of effect on mortality and lack of difference between the different preparations and doses of polyvalent IVIG do not support a true biologic effect of immunoglobulins in the context of BMT. These agents are associated with adverse effects, a higher rate of VOD, and are costly. Current evidence does not support their use as routine prophylaxis for patients undergoing BMT or HSCT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Pia Raanani, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, Ofer Shpilberg

Provision of study materials or patients: Pia Raanani, Anat Gafter-Gvili

Collection and assembly of data: Pia Raanani, Anat Gafter-Gvili, Mical Paul

Data analysis and interpretation: Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, Ofer Shpilberg

Manuscript writing: Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, Ofer Shpilberg

Final approval of manuscript: Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, Ofer Shpilberg

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Acknowledgment

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Appendix

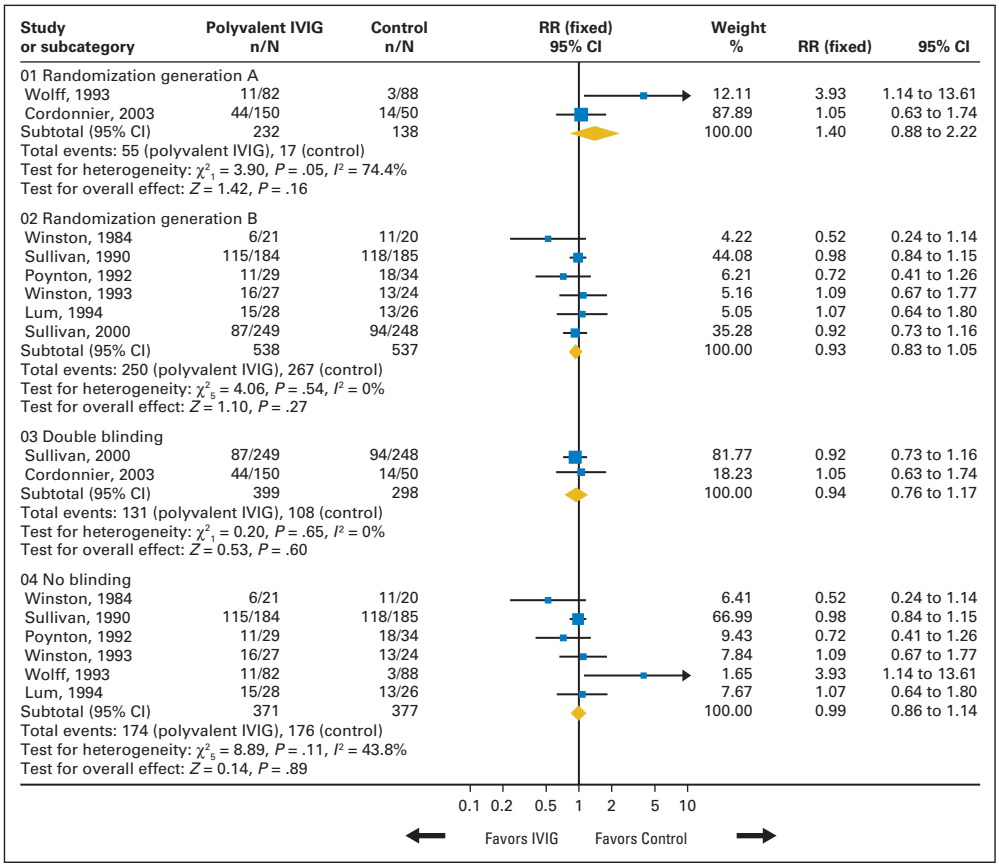

Fig A1. All-cause mortality at end of follow-up in trials comparing polyvalent immunoglobulins (IVIG) versus placebo or no treatment-sensitivity analysis by randomization generation and double blinding. Randomization generation: A, adequate; B = unclear (Sullivan KM, Kopecky KJ, Jocom J, et al: N Engl J Med 323:705-712, 1990; Poynton CH, Jackson S, Fegan C, et al: Bone Marrow Transplant 9:451-457, 1992; Cordonnier C, Chevret S, Legrand M, et al: Ann Intern Med 139:8-18, 2003; Winston DJ, Pollard RB, Ho WG, et al: Ann Intern Med 97:11-18, 1982; Winston DJ, Ho WG, Bartoni K, et al: Bone Marrow Transplant 12:283-288, 1993; Lum L, Bitonti O, Jin NR, et al: Exp Hematol 22:680, 1994; Sullivan K, Seidel K, Jocom J, et al: J Clin Oncol:181, 2000; Wolff SN, Fay JW, Herzig RH, et al: Ann Intern Med 118:937-942, 1993). RR, relative risk.