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Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock (Review)

Alejandria MM, Lansang MAD, Dans LF, Mantaring III JB

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[Intervention Review]

Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock

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ABSTRACT

Background

Mortality from sepsis and septic shock remains high. Results of trials on intravenous immunoglobulins (IVIG) as adjunctive therapy for sepsis have been conflicting. This is an update of a Cochrane review that was originally published in 1999 and updated in 2002 and 2010.

Objectives

To estimate the effects of IVIG as adjunctive therapy in patients with bacterial sepsis or septic shock on mortality, bacteriological failure rates, and duration of stay in hospital.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 6), MEDLINE (1966 to December 2012), and EMBASE (1988 to December 2012). We contacted investigators in the field for unpublished data. The original search was performed in 1999 and updated in 2002 and 2008.

Selection criteria

We included randomized controlled trials comparing IVIG (monoclonal or polyclonal) with placebo or no intervention in patients of any age with bacterial sepsis or septic shock.

Data collection and analysis

Two authors independently assessed the studies for inclusion and undertook methodologic quality assessment and data abstraction. We conducted pre-specified subgroup analyses by type of immunoglobulin preparation.

Main results

We included 43 studies that met our inclusion criteria in this updated review out of 88 potentially eligible studies. The studies included a large polyclonal IVIG trial in neonates that was concluded in 2011 and classified as ongoing in the 2010 version of this review. Pooled analysis of polyclonal and monoclonal IVIG was not done due to clinical heterogeneity. Subgroup analysis of 10 polyclonal IVIG trials (n = 1430) and seven trials on IgM-enriched polyclonal IVIG (n = 528) showed significant reductions in mortality in adults with sepsis compared to placebo or no intervention (relative risk (RR) 0.81; 95% confidence interval (CI) 0.70 to 0.93 and RR 0.66; 95% CI 0.51 to 0.85, respectively). Subgroup analysis of polyclonal IVIG in neonates, which now includes the recently concluded large polyclonal IVIG trial,

showed no significant reduction in mortality for standard IVIG (RR 1.00; 95% CI 0.92 to 1.08; five trials, n = 3667) and IgM-enriched polyclonal IVIG (RR 0.57; 95% CI 0.31 to 1.04; three trials, n = 164). Sensitivity analysis of trials with low risk of bias showed no reduction in mortality with polyclonal IVIG in adults (RR 0.97; 95% CI 0.81 to 1.15; five trials, n = 945) and neonates (RR 1.01; 95% CI 0.93 to 1.09; three trials, n = 3561). Mortality was not reduced among patients (eight trials, n = 4671) who received anti-endotoxin antibodies (RR 0.99; 95% CI 0.91 to1.06) while anti-cytokines (nine trials, n = 7893) demonstrated a marginal reduction in mortality (RR 0.92; 95% CI 0.86 to 0.97).

Authors' conclusions

Polyclonal IVIG reduced mortality among adults with sepsis but this benefit was not seen in trials with low risk of bias. Among neonates with sepsis, there is sufficient evidence that standard polyclonal IVIG, as adjunctive therapy, does not reduce mortality based on the inclusion of the large polyclonal IVIG trial on neonates. For Ig-M enriched IVIG, the trials on neonates and adults were small and the totality of the evidence is still insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IVIGs remains experimental.

PLAIN LANGUAGE SUMMARY

Intravenous immunoglobulins for treating patients with severe sepsis and septic shock

Sepsis is the inflammatory response of the body to severe infection, which can be caused by a variety of micro-organisms including bacteria, viruses and fungi. Signs of sepsis include fever, hypothermia, rapid heart rate and respiration; and a laboratory finding of increased or decreased white blood cell count. Deaths as a result of sepsis and septic shock remain high despite giving antibiotics, especially if the functions of a persons's vital organs such as the lungs, heart and kidneys are affected. Several studies have looked into other agents than antibiotics to help the body fight the effects of sepsis. Intravenous immunoglobulin preparations contain antibodies that help the body to neutralize bacterial toxins. There are two types of preparations. These are polyclonal immunoglobulins that contain several antibodies directed at endotoxin and inflammatory mediators, and monoclonal immunoglobulins which target a specific inflammatory mediator or antigen. Intravenous immunoglobulins are blood products, specifically pooled sera derived from human donor blood.

For this updated Cochrane review, we searched the medical literature databases to January 2012. We included 43 randomized controlled trials (RCTs); 25 were RCTs of polyclonal intravenous immunoglobulins (IVIGs) with 17 in adults (1958 participants) and eight in newborn infants (3831 participants) including a large polyclonal IVIG trial on infants with sepsis that was published in 2011. The remaining 18 trials (a total of 13,413 participants) were of monoclonal antibodies. Both standard and immunoglobulin M (IgM)-enriched polyclonal immunoglobulins decreased the number of deaths in adults but not in infants. However, no reductions in adult deaths were seen with polyclonal IVIG using high quality trials only. Among newborn infants with sepsis, there is definitive evidence that standard polyclonal IVIG does not reduce the number of deaths. In the monoclonal immunoglobulin trials, anti-endotoxin antibodies showed no benefit while the anti-cytokines showed a very small reduction in deaths among adults with sepsis.

The polyclonal immunoglobulin trials in adults were small compared to the trials of monoclonal agents. The reduction in deaths observed with polyclonal IgM-enriched preparations as add-on therapy for sepsis needs to be confirmed in large studies that use high quality methods.

Summary of findings for the main comparison. Polyclonal intravenous immunoglobulin (IVIG) versus placebo or no intervention for sepsis, severe sepsis and septic shock

Polyclonal IVIG versus placebo or no intervention for sepsis, severe sepsis and septic shock

Patient or population: neonates with sepsis, severe sepsis and septic shock
Intervention: polyclonal IVIG
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo or no intervention	Polyclonal IVIG			
All-cause mortality, neonates, standard polyclonal IVIG	**Study population**		**RR 1** (0.92 to 1.08)	3667 (5 studies)	⊕⊕⊕⊖ **moderate**[1]
	380 per 1000	**380 per 1000** (349 to 410)			
	Moderate				
	280 per 1000	**280 per 1000** (258 to 302)			
All-cause mortality, neonates, IgM-enriched polyclonal IVIG	**Study population**		**RR 0.57** (0.31 to 1.04)	164 (3 studies)	⊕⊕⊖⊖ **low**[2,3]
	274 per 1000	**156 per 1000** (85 to 285)			
	Moderate				
	267 per 1000	**152 per 1000** (83 to 278)			
Low risk of bias neonate studies, mortality all-cause - standard IVIG	**Study population**		**RR 1.01** (0.93 to 1.09)	3561 (3 studies)	⊕⊕⊕⊕ **high**
	387 per 1000	**391 per 1000** (360 to 421)			

Moderate		
294 per 1000	**297 per 1000** (273 to 320)	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Two studies are of low quality (Chen 1996; Shenoi 1999)
[2] Two studies are of low quality (Erdem; Samatha)
[3] Wide confidence intervals, small studies

Summary of findings 2. Polyclonal intravenous immunoglobulin (IVIG) versus placebo or no intervention for sepsis, severe sepsis and septic shock

Polyclonal IVIG versus placebo or no intervention for sepsis, severe sepsis and septic shock

Patient or population: adult patients with sepsis, severe sepsis and septic shock
Intervention: polyclonal IVIG
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo or no intervention	Polyclonal IVIG			
All-cause mortality, adults, standard polyclonal IVIG	**Study population**		**RR 0.81** (0.7 to 0.93)	1430 (10 studies)	⊕⊕⊕⊖ **moderate**[1]
	365 per 1000	**296 per 1000** (256 to 340)			
	Moderate				
	423 per 1000	**343 per 1000** (296 to 393)			

All-cause mortality, adults, IgM-enriched polyclonal IVIG	**Study population**		**RR 0.66** (0.51 to 0.85)	528 (7 studies)	⊕⊕⊕⊖ **moderate**[2]
	375 per 1000	**247 per 1000** (191 to 318)			
	Moderate				
	412 per 1000	**272 per 1000** (210 to 350)			
Low risk of bias adult studies, by type of polyclonal IVIG, mortality all-cause	**Study population**		**RR 0.97** (0.81 to 1.15)	945 (5 studies)	⊕⊕⊕⊕ **high**
	354 per 1000	**344 per 1000** (287 to 408)			
	Moderate				
	364 per 1000	**353 per 1000** (295 to 419)			
Low risk of bias adult studies, mortality all-cause - standard IVIG	**Study population**		**RR 1.02** (0.84 to 1.24)	683 (3 studies)	⊕⊕⊕⊕ **high**
	367 per 1000	**374 per 1000** (308 to 455)			
	Moderate				
	364 per 1000	**371 per 1000** (306 to 451)			
Low risk of bias adult studies, mortality all-cause - IgM-enriched IVIG	**Study population**		**RR 0.82** (0.56 to 1.19)	262 (2 studies)	⊕⊕⊕⊖ **moderate**[3]
	323 per 1000	**265 per 1000** (181 to 384)			
	Moderate				
	382 per 1000	**313 per 1000** (214 to 455)			

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Only 3 studies on standard polyclonal IVIG are of high quality (Burns 1991; Darenberg 2003; Werdan 2007)
[2] Only 2 studies on IgM-enriched IVIG are of high quality (Hentrich 2006; Rodriguez 2005)
[3] There are only 2 studies, summary effect with wide confidence intervals

Summary of findings 3. Monoclonal antibodies compared to placebo for sepsis, severe sepsis, septic shock

Anti-endotoxins compared to placebo for sepsis, severe sepsis, septic shock

Patient or population: patients with sepsis, severe sepsis, septic shock
Settings:
Intervention: anti-endotoxins
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Anti-endotoxins			
Anti-endotoxins versus placebo, all-cause mortality	**Study population**		**RR 0.92** (0.79 to 1.06)	4676 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
	369 per 1000	**340 per 1000** (292 to 391)			
	Moderate				
	406 per 1000	**374 per 1000** (321 to 430)			
Anti-endotoxin E5 versus placebo, all- cause mortality	**Study population**		**RR 0.98** (0.88 to 1.1)	1975 (4 studies)	⊕⊕⊕⊖ **moderate**[3]
	385 per 1000	**377 per 1000** (338 to 423)			
	Moderate				
	406 per 1000	**398 per 1000**			

		(357 to 447)			
Anti-endotoxin - HA-1A versus placebo, all-cause mortality	**Study population**		**RR 0.8** (0.54 to 1.2)	2668 (3 studies[4])	⊕⊖⊖⊖ **very low**[4,5]
	356 per 1000	**285 per 1000** (192 to 428)			
	Moderate				
	356 per 1000	**285 per 1000** (192 to 427)			
Anti-endotoxins Anti-LPS versus placebo, all-cause mortality	**Study population**		**RR 0.15** (0.02 to 1.06)	33 (1 study)	⊕⊕⊖⊖ **low**[6]
	474 per 1000	**71 per 1000** (9 to 502)			
	Moderate				
	474 per 1000	**71 per 1000** (9 to 502)			
Sensitivity analysis by quality, anti-endotoxin, all-cause mortality	**Study population**		**RR 1.01** (0.94 to 1.09)	4443 (6 studies[3])	⊕⊕⊕⊖ **moderate**[3]
	364 per 1000	**367 per 1000** (342 to 397)			
	Moderate				
	380 per 1000	**384 per 1000** (357 to 414)			
Anti-endotoxin, all-cause mortality - low risk of bias studies	**Study population**		**RR 0.67** (0.42 to 1.05)	269 (1 study)	⊕⊕⊕⊖ **moderate**[6]
	275 per 1000	**184 per 1000** (116 to 289)			
	Moderate				
	275 per 1000	**184 per 1000** (115 to 289)			
Anti-endotoxin, all-cause mortality - unclear risk of bias	**Study population**		**RR 1.03** (0.95 to 1.11)	4174 (5 studies)	⊕⊕⊕⊖ **moderate**[3]

	370 per 1000	**381 per 1000** (351 to 410)
	Moderate	
	403 per 1000	**415 per 1000** (383 to 447)

*The basis for the **assumed risk** is the median control group risk across the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Five studies with unclear allocation concealment
[2] There is a significant subgroup difference
[3] Unclear allocation concealment
[4] Two studies with unclear allocation concealment
[5] Significant heterogeneity of the three trials
[6] One trial only, with wide confidence interval

Summary of findings 4. Monoclonal antibodies compared to placebo for sepsis, severe sepsis, septic shock

Anti-cytokines compared to placebo for sepsis, severe sepsis, septic shock

Patient or population: patients with sepsis, severe sepsis, septic shock
Settings:
Intervention: anti-cytokines
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Anti-cytokines			
Anti-cytokines versus placebo, all-cause mortality	**Study population**		**RR 0.92** (0.86 to 0.97)	7893 (9 studies)	⊕⊕⊕⊖ **moderate**[1]
	377 per 1000	**347 per 1000**			

		(324 to 366)			
	Moderate				
	395 per 1000	**363 per 1000** (340 to 383)			
Anticytokine - anti-TNF-alpha versus placebo, all-cause mortality	**Study population**		**RR 0.92** (0.87 to 0.99)	6200 (6 studies)	⊕⊕⊕⊖ **moderate**[2]
	382 per 1000	**352 per 1000** (333 to 378)			
	Moderate				
	405 per 1000	**373 per 1000** (352 to 401)			
Anti-cytokines - human interleukin-1receptor antagonist versus placebo, all-cause mortality	**Study population**		**RR 0.88** (0.76 to 1.01)	1693 (3 studies)	⊕⊕⊕⊖ **moderate**[2]
	355 per 1000	**313 per 1000** (270 to 359)			
	Moderate				
	364 per 1000	**320 per 1000** (277 to 368)			
Sensitivity analysis by quality, anti-cytokine, all-cause mortality	**Study population**		**RR 0.91** (0.86 to 0.97)	7752 (7 studies)	⊕⊕⊕⊖ **moderate**[3]
	376 per 1000	**342 per 1000** (323 to 365)			
	Moderate				
	364 per 1000	**331 per 1000** (313 to 353)			
Anti-cytokine, all-cause mortality - low risk of bias studies	**Study population**		**RR 0.92** (0.86 to 0.99)	5065 (3 studies)	⊕⊕⊕⊕ **high**
	388 per 1000	**357 per 1000** (334 to 384)			
	Moderate				

	395 per 1000	**363 per 1000** (340 to 391)			
Anti-cytokine, all-cause mortality - uncertain risk of bias	**Study population**		**RR 0.89** (0.8 to 1)	2687 (4 studies)	⊕⊕⊕⊖ **moderate**[3]
	347 per 1000	**309 per 1000** (278 to 347)			
	Moderate				
	351 per 1000	**312 per 1000** (281 to 351)			

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Six studies with unclear allocation concealment
[2] Three studies with unclear allocation concealment
[3] Unclear allocation concealment 4 studies

BACKGROUND

Description of the condition

Sepsis is a systemic inflammatory response of the body to severe infection caused by various micro-organisms including bacteria, viruses and fungi. It is detected through a constellation of signs such as fever, hypothermia, tachycardia and rapid respiration; and a laboratory finding of an increased or decreased white blood cell count. Overwhelming sepsis can lead to multiorgan dysfunction and shock. Despite the development of new and effective antibiotics, hospital mortality from sepsis ranges from 18% in a developed country (Sundararajan 2006) to 87% in a developing country setting (Tanriover 2006), with a stepwise increase in mortality as sepsis progresses to septic shock (Rangel-Frausto 1995). Two tertiary hospitals in metropolitan Manila, Philippines reported mortality rates of 34% and 50% among sepsis patients (Alejandria 2000; Villa 1995), which increased to 59% among patients with severe sepsis (Taguiang-Abu 2008). A recent multinational prospective cohort study on the management of severe sepsis in 150 intensive care units in 16 Asian countries reported a hospital mortality of 44.5% out of 1285 adult patients (Phua 2011).

Description of the intervention

The cascade of harmful effects from sepsis and septic shock has been postulated to be largely due to the lipid-A component of the endotoxin molecule in gram-negative bacteria. Thus the use of antibodies against different components of the endotoxin molecule as adjunctive therapy for sepsis has been the target of various investigations. A number of these studies have been randomized controlled trials of various types of human immunoglobulin preparations in the treatment of patients with septic shock. The most commonly used interventions in these studies were monoclonal and polyclonal immunoglobulin preparations given intravenously. Monoclonal preparations contain immunoglobulins developed from a single cell line targeting a specific antigen; while polyclonal preparations are from pooled human sera containing different immunoglobulins (Ig), mainly IgG and IgM, not necessarily directed at specific antigen sites. Intravenous immunoglobulins are biological products derived from human blood.

How the intervention might work

It is postulated that neutralizing and opsonizing antibodies contained in polyclonal immunoglobulin preparations inactivate bacterial endotoxins and exotoxins, stimulate leukocytes, and increase serum bactericidal activity. It is also hypothesized that immunoglobulins interfere with cytokine effects by modulating the release of cytokine and cytokine antagonists by endotoxins, attenuating the effects of the complement cascade (Werdan 2001). Results from trials on the effects of the different types of immunoglobulin preparations in reducing mortality from septic shock have been conflicting. A meta-analysis (Lacy 1995) reviewing the prophylactic effect of IVIG on infection in preterm infants did not recommend its routine use. Another meta-analysis (Jenson 1997), however, concluded that there was a significant benefit to giving IVIG shortly after birth in preventing sepsis among premature low birth-weight newborns and in reducing deaths among neonates with early-onset sepsis. An update of a Cochrane review (Ohlsson 2013) concluded that there is insufficient evidence to support the routine use of polyclonal IVIG for infants with suspected or proven neonatal infection.

Adverse effects from IVIG therapy have also been reported and can be classified into three types according to their onset. These are immediate, delayed, and late onset. Immediate adverse effects occur during infusion, for example anaphylactoid reactions; delayed adverse effects occur hours or days after infusion, for example pulmonary, renal, haematologic and neurologic events; and late adverse effects include transmission of infectious agents such as hepatitis C and prion diseases (Nydegger 1999).

Why it is important to do this review

The use of IVIG in sepsis has major implications for developing countries such as the Philippines where sepsis is a common cause of hospital mortalities and where medical practitioners use IVIG indiscriminately for both prophylaxis and the treatment of infections and sepsis. A survey of prescribing patterns for immunoglobulin use among paediatricians in three hospitals in Manila, Philippines showed that neonatal sepsis was the third most common condition for which IVIG was used (Zabala 1999). Considering the high cost of IVIG, potential adverse effects, and conflicting reports on its benefits in sepsis, we should continually assess the evidence from randomized controlled trials.

This review updates our existing Cochrane review, which was first published in 1999 and was updated in 2002 (Alejandria 2002) and 2010. The 2010 update included the large polyclonal IVIG trial on adults that was conducted in 1995 (Werdan 1997 abstract) and published 10 years after its completion (Werdan 2007). This was the main point of difference between our 2002 review (Alejandria 2002) and the subsequent meta-analysis by Pildal and Goetzsche in 2004 (Pildal 2004). In this update (2013) we have included the large polyclonal IVIG trial on neonates which was completed and published in 2011 (Brocklehurst 2011).

OBJECTIVES

To estimate the effects of intravenous immunoglobulin (IVIG) as adjunctive therapy in patients with bacterial sepsis or septic shock on mortality, bacteriological failure rates, and duration of stay in hospital.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) comparing IVIG with a control group that received placebo or no intervention. We excluded quasi-randomized studies.

Types of participants

We included studies on patients of any age with sepsis or septic shock caused by bacteria.

The 1992 and 2001 consensus conference definitions of sepsis, severe sepsis and septic shock (Bone 1992; Levy 2003) are as follows.

Sepsis is the presence of two or more of the following systemic inflammatory responses to a documented infection: a)

temperature > 38 °C or < 36 °C; b) heart rate > 90 beats/min; c) respiratory rate > 20 breaths/min or $PaCo_2$ < 32 mmHg; d) white blood cell count > 12,000/mm, < 4000/mm, or > 10% immature forms.

Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion abnormalities may include lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock is a subset of severe sepsis, defined as persistence of sepsis-induced hypotension despite adequate fluid resuscitation.

Types of interventions

The experimental intervention was any monoclonal or polyclonal intravenous immunoglobulin (IVIG) for the treatment of sepsis and septic shock.
The control group received placebo or no immunoglobulin.

Types of outcome measures

Primary outcomes

1. All-cause mortality at the end of the follow-up period
2. Short-term mortality: mortality measured at 30 days (30-day mortality)
3. Long-term mortality: mortality measured at time periods greater than 30 days

Secondary outcomes

1. Bacteriological failure rate
2. Development of organ failure
3. Length of hospital stay among survivors
4. Mortality from septic shock
5. Adverse effects

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2012, Issue 6) (using the search terms listed in Appendix 1); MEDLINE (1966 to December 2012) (Appendix 2); EMBASE (1988 to December 2012) (Appendix 3). The topic search terms were used in combination with the Cochrane highly sensitive search strategy for identifying RCTs.

We used the following free text and MeSH terms to search all trials registers and databases: immunoglobulin* near (monoclon* or polyclon*), IVIG, immunoglobulins-intravenous, sepsis, septic shock, septicaemia or septicaemia.

We did not apply language restrictions.

Searching other resources

We reviewed citations in the trial reports identified by the above methods. Investigators or organizations working in this field were also contacted for more information on published and unpublished RCTs. We requested extraction of information from foreign language trials that met the inclusion criteria.

Data collection and analysis

Selection of studies

Two authors (MAL, MMA) independently assessed the titles (and abstracts when available) identified in the search printouts for eligibility. Articles that might have met the selection criteria or could have referred to a possible trial were all retrieved and examined.

Data extraction and management

Data abstraction forms and operational definitions for outcomes and explanatory variables were developed. Two authors (LFD, JVM) independently abstracted information from each study prior to pooling of results. Data abstraction included the time period and geographical location of the study, baseline patient characteristics, inclusion and exclusion criteria, type of IVIG preparation and the dosing regimen, and the type of placebo used, if any. Information on each of the following outcome measures were also abstracted: mortality, bacteriological failures, duration of hospitalisation, and the number or per cent of affected patients.

Assessment of risk of bias in included studies

Two authors (LFD, JVM) independently appraised the quality of the included studies by assessing allocation concealment, generation of the allocation sequence, and inclusion of all randomized participants. The 2010 update of this review used the standards set by the Cochrane Anaesthesia Group while the previously published version of this review (Alejandria 2002) used the criteria set by the Cochrane Infectious Diseases Group, available on the Group Module in *The Cochrane Library*. In addition to the standards set by both review groups, we assessed the comparability of the baseline characteristics and the care received by the treatment and control groups in terms of co-interventions, frequency of follow up, and general quality of care.

In this update, the risk of bias assessment was updated using the Cochrane Collaboration's tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following domains were used: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias, for example comparability of baseline characteristics and the care received by the treatment and control groups in terms of co-interventions, frequency of follow up, and general quality of care. Judgments on the risk of bias for each component were as follows.

1. Generation of allocation sequence

- Low risk: if appropriate methods such as random numbers generated by a computer or table of random numbers, drawing of lots, coin toss, or throwing dice were used.
- High risk: if sequences such as case record number; date of birth; day, month, or years of admission were used.
- Unclear risk: if the methods were not described.

2. Concealment of allocation

- Low risk: if measures were used to prevent foreknowledge of assignment, such as centralized randomization; or numbered, sealed, opaque envelopes.

- HIgh risk: if researchers and participants could foresee an upcoming assignment e.g. by alternation.
- Unclear risk: if the methods were not described.

3. Blinding of participants and personnel

- Low risk: no blinding, or incomplete blinding but review authors judge that the outcome is not likely to be influenced by lack of blinding, or blinding of participants and key personnel ensured and unlikely that the blinding could have been broken.
- High risk: no blinding, or incomplete blinding and the outcome is likely to be influenced by lack of blinding, or blinding of participants and key personnel attempted but likely that the blinding could have been broken and the outcome is likely to be influenced by lack of blinding.
- Unclear risk: insufficient information to permit judgment, or the study did not address the outcome.

4. Blinding of outcome assessment

- Low risk: blinding of outcome assessment ensured and unlikely that blinding could have been broken; outcome detection methods are the same for both groups.
- High risk: no blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding, or blinding of outcome assessment done but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.
- Unclear risk: insufficient information to permit judgment.

5. Incomplete outcome data

- Low risk: no missing outcome data; reasons for missing data unlikely to be related to true outcome; missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups; for dichotomous data, the proportion of missing outcomes compared with observed event risk not likely to have a clinically relevant impact on the intervention effect estimate; for continuous data, plausible effect size among missing outcomes not likely to have a clinically relevant impact on the observed effect size; intention-to-treat analysis was done.
- High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous data, proportion of missing outcomes compared with observed event risk likely to cause clinically relevant bias in the intervention effect estimate; for continuous data, plausible effect size among missing outcomes likely to cause a clinically relevant bias in the observed effect size; efficacy analysis done with substantial departure of the intervention received from that assigned during randomization; intention-to-treat analysis was not done.
- Unclear risk: insufficient reporting of attrition and exclusions to permit judgment (e.g. number of participants randomized not stated; reasons for missing data not stated).

6. Selective outcome reporting

- Low risk: study protocol is available and all of the study's pre-specified outcomes that are of interest in the review were reported in a pre-specified way; study protocol is not available but published reports include all expected outcomes, including those that were pre-specified.
- HIgh risk: not all of the study's pre-specified primary outcomes were reported; one or more primary outcomes are reported using measurements, analysis methods or subsets of the data that were not pre-specified; one or more reported primary outcomes were not pre-specified, unless clear justification is provided; one or more outcomes of interest in the review are reported incompletely; failure to include a key outcome that would be expected to have been reported in such a study.
- Unclear risk: insufficient information to permit judgment.

7. Other sources of bias

- Low risk: study appears free of other sources of bias, e.g. treatment and control groups were treated equally in terms of other therapies and co-interventions received, frequency of follow up, and general quality of care; the magnitude of any difference in baseline characteristics of the treatment and control groups was not significant in terms of known determinants of outcome.
- HIgh risk: study had a potential source of bias related to study design used or has been claimed to be fraudulent; study had significant differences between the treatment and control groups in terms of baseline characteristics that are known predictors of outcome; overt differences in the general quality of care received by the groups, such as differential administration of co-interventions.
- Unclear risk: insufficient information to assess whether an important risk of bias exists, or insufficient evidence or rationale that an identified problem will introduce bias.

Measures of treatment effect

For statistical analysis of dichotomous outcomes, relative risk (RR) and risk difference (RD) with 95% confidence interval (CI) were calculated using the fixed-effect model. For continuous outcomes, the mean difference (MD) with 95% CI was calculated.

Dealing with missing data

We contacted authors of studies with unclear or missing data.

Assessment of heterogeneity

To test for statistical heterogeneity across studies we used the Chi^2 statistic. A value of $P < 0.10$ was used to reject the null hypothesis of homogeneity between studies. To quantify the degree of inconsistency, we used the I^2 statistic.

Assessment of reporting biases

We constructed a funnel plot to assess for evidence of publication bias.

Data synthesis

We synthesised and analysed the data using Review Manager 5.2 (RevMan 5.2). We combined dichotomous data using the Mantel-Haenszel method, and we analysed continuous data using the inverse variance approach. Depending on the degree of heterogeneity of the data, we used either a fixed-effect model or a random-effects model (Der Simonian and Laird model).

Subgroup analysis and investigation of heterogeneity

Recognizing that polyclonal and monoclonal IVIG preparations differ structurally and that they act through different immunopathologic mechanisms, a priori subgroup analyses were planned to compare the following explanatory variables: polyclonal IVIG versus placebo or no intervention; monoclonal IVIG versus placebo or no intervention; severity of sepsis; and duration of sepsis. We performed additional subgroup analyses post hoc according to the type of polyclonal IVIG and age group (standard IVIG and immunoglobulin M (IgM)-enriched for adults and neonates) and types of monoclonal antibodies (anti-endotoxins and anti-cytokines). A subgroup analysis of adult and neonatal polyclonal IVIG trials was performed because of the recognized inherent physiologic, pathophysiologic and prognostic differences between adults and neonates with sepsis. No subgroup analysis was done for the monoclonal antibody studies according to study participant (adult or neonate) because all the trials were performed on adults except for one study done with children. To explore the effects of patients' characteristics on IVIG effects, post hoc subgroup analysis of polyclonal trials on adults with surgical and non-surgical conditions was done.

Sensitivity analysis

We also conducted sensitivity analyses of the polyclonal and monoclonal studies by removing the trials with high risk of bias and by doing random-effects meta-analysis.

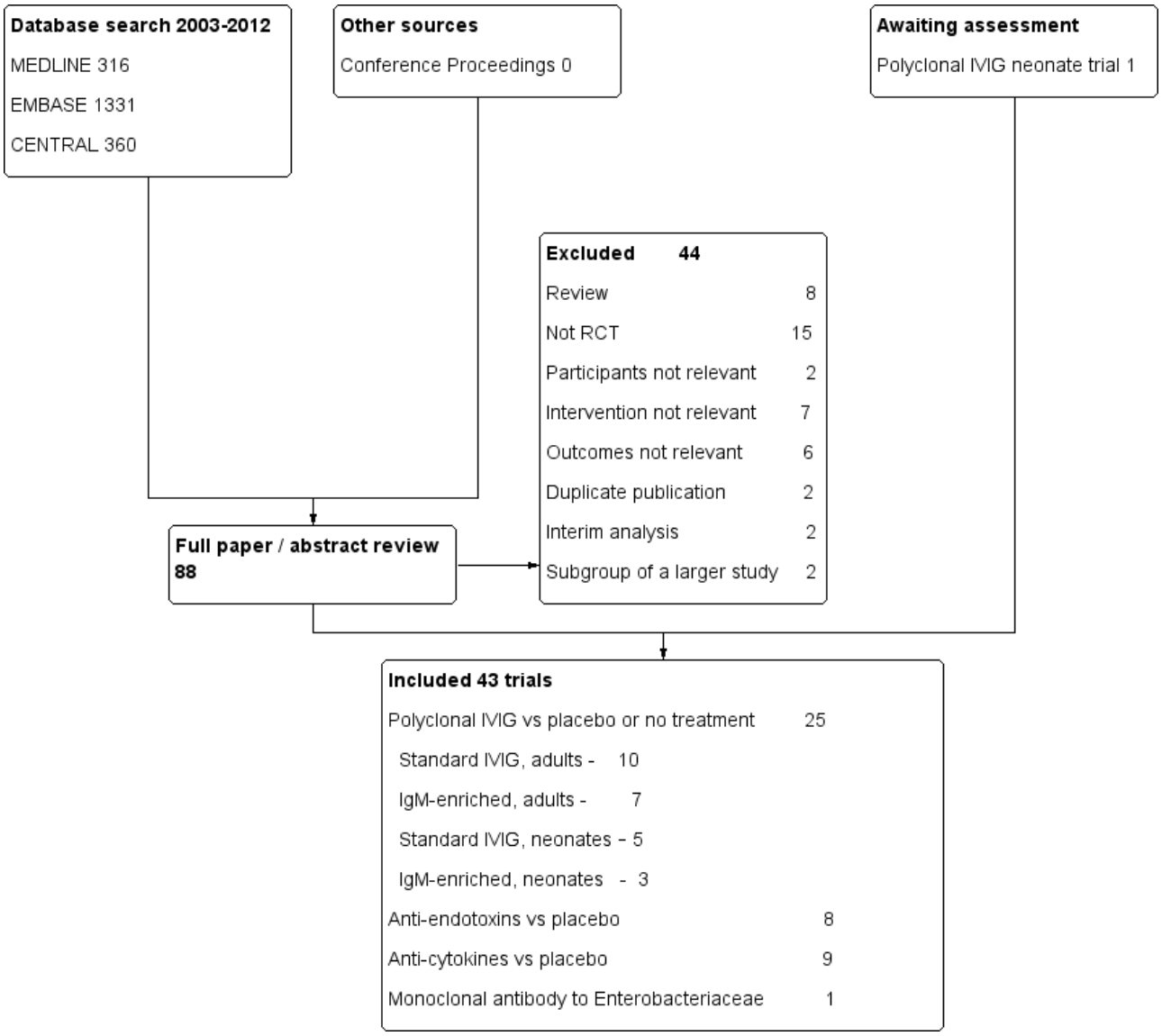
RESULTS

Description of studies

Results of the search

We retrieved 88 potentially eligible studies, 43 of which fulfilled the inclusion criteria. Of the 25 studies on polyclonal IVIG, 17 were on adults (10 standard IVIG, 7 IgM-enriched) and eight were on neonates (5 standard IVIG, 3 IgM-enriched). There were 18 studies on monoclonal preparations, eight on anti-endotoxins, nine on anti-cytokines, and one study on a human monoclonal antibody to Enterobacteriaceae common antigen. The search flow diagram shows the results of the search from 2003 to 2012 (Figure 1).

Figure 1. Search flow diagram.



Included studies

Details of the included studies are provided in the table Characteristics of included studies. Forty-three published studies met the inclusion criteria.

Participants

The clinical trials were performed mainly in intensive care units and academic medical centres, in 23 countries. The polyclonal IVIG trials were conducted in Argentina, Australia, Belgium, Denmark, Finland, Germany, Greece, Ireland, Japan, India, Ireland, Italy, Mexico, Netherlands, New Zealand, Norway, Saudi Arabia, Serbia, Sweden, Spain, Taiwan, Turkey, United Kingdom, and the United States of America. The monoclonal trials were mostly multi-centre studies conducted in Austria, Belgium, Canada, England, France, Germany, Greece, Israel, Italy, the Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, and the United States of America.

There were eight polyclonal IVIG trials on neonatal sepsis (Brocklehurst 2011; Chen 1996; Erdem 1993; Haque 1988; Mancilla-Ramirez 1992; Samatha 1997; Shenoi 1999; Weisman 1992); one anti-endotoxin trial on children with meningococcal septic shock (Derkx 1999); five polyclonal IVIG trials on adults with post-operative sepsis (Dominioni 1996; Grundmann 1988; Rodriguez 2005; Wesoly 1990; Yakut 1998); one polyclonal IVIG trial on adults with streptococcal toxic shock syndrome (Darenberg 2003); two polyclonal IVIG trials on neutropenic patients with haematologic malignancies and sepsis syndrome or septic shock (Behre 1995; Hentrich 2006); and one anti-endotoxin study on obstetric and gynaecologic patients with septic shock (Lachman 1984). The rest of the trials involved adults with sepsis or septic shock, either of gram-positive or gram-negative etiology.

The polyclonal IVIG trials on neonatal sepsis included pre-term infants (Brocklehurst 2011; Erdem 1993; Haque 1988; Weisman 1992); full-term and pre-term infants (Chen 1996; Samatha 1997; Shenoi 1999); and full-term neonates (Mancilla-Ramirez 1992).

Most of the polyclonal IVIG trials on adults included participants who were aged 18 years and above, except for some trials which had participants < 18 years old (Dominioni 1996; Grundmann 1988; Masaoka 2000; Schedel 1991; Tugrul 2002). The monoclonal studies included adults 18 years and above except for one anti-endotoxin (HA-1A) trial, which included children aged from three months up to 18 years (Derkx 1999).

Interventions

The IVIG preparations used were monoclonal (18 studies) or polyclonal immunoglobulins (25 studies).

The monoclonal preparations were:

1. anti-endotoxins such as E5 (Angus 2000; Bone 1995; Greenberg 1992; Greenman 1991), anti-lipopolysaccharide (anti-LPS) (Lachman 1984), and HA-1A (Derkx 1999; McCloskey 1994; Ziegler 1991);
2. anti-cytokines such as interleukin-1 (IL-1) (Fisher 1994a; Fisher 1994b; Opal 1997) and anti-tumour necrosis factor (TNF) alpha (Abraham 1995; Abraham 1998; Cohen 1996; Dhainaut 1995; Panacek 2004; Reinhart 1996); and
3. human monoclonal antibody to Enterobacteriaceae common antigen (Albertson 2003).

Polyclonal IVIG preparations were standard IVIG in 10 trials on adults (Burns 1991; Darenberg 2003; De Simone 1988; Dominioni 1991; Grundmann 1988; Just 1986; Lindquist 1981; Masaoka 2000; Werdan 2007; Yakut 1998) and five trials on neonates (Brocklehurst 2011; Chen 1996; Mancilla-Ramirez 1992; Shenoi 1999; Weisman 1992), and IgM-enriched immunoglobulin in seven trials on adults (Behre 1995; Hentrich 2006; Karatzas 2002; Rodriguez 2005; Tugrul 2002; Wesoly 1990) and three trials on neonates (Erdem 1993; Haque 1988; Samatha 1997).

For neonates, the dose of standard polyclonal IVIG ranged from 500 mg/kg as a single infusion over two hours (Chen 1996; Haque 1988; Mancilla-Ramirez 1992; Weisman 1992) to 500 mg/kg infused over four to six hours then repeated 48 hours later (Brocklehurst 2011) and up to 1 g/kg for three days (Shenoi 1999); while IgM-enriched IVIG was given at 5 ml/kg/day for three days (Erdem 1993; Samatha 1997).

For adults, the dose of polyclonal IVIG varied depending on the type of IVIG, from 250 mg/kg over two days (Intraglobin) to 400 mg/kg/day for three days (Sandoglobin), and 1 g/kg on the first day then 500 mg/kg on days two and three (Endobulin). For Ig-M enriched IVIG (Pentaglobin) the dose used was 1300 ml infused within 72 hours (Behre 1995; Hentrich 2006).

Outcomes

All polyclonal and monoclonal trials reported on all-cause mortality as a main outcome except for one polyclonal study on neonates (Erdem 1993), which reported mortality from sepsis only. One polyclonal study on adults did not report mortality but data were obtained through communication with the authors (Masaoka 2000).

The polyclonal IVIG trials on neonates did not specify the cut-off and follow-up periods for mortality except for one trial which had weekly follow ups for six weeks after discharge (Chen 1996) and another which reported mortality at 56 days (Weisman 1992). The large multi-centre trial (Brocklehurst 2011) reported death or major disability at two years as the primary outcome and death in hospital as a secondary outcome.

Only two polyclonal trials in adults reported long-term mortality, at 60 days (Hentrich 2006) and 180 days (Darenberg 2003). The rest of the trials either reported short-term mortality, at 28 days (Behre 1995; Darenberg 2003; Karatzas 2002; Tugrul 2002; Werdan 2007) or 30 days (Rodriguez 2005), or did not specify the cut-off and follow-up periods. One trial in which the primary outcome was an increase in platelet count had a nine-day follow up (Burns 1991) while another trial where the main outcome was defervescence and eradication of symptoms had a seven-day follow up only (Masaoka 2000).

Monoclonal trials reported short-term all-cause mortality at 28 days except for trials which reported on 14-day (McCloskey 1994), 21-day (Greenberg 1992), and 30-day (Bone 1995; Greenman 1991) mortality. Only one monoclonal HA-1A trial (Derkx 1999) reported on long-term mortality, at 56 days.

Sample size

Of the eight polyclonal IVIG studies on neonates, one was a large multi-centre, multi-country trial (Brocklehurst 2011) and seven were small studies, mainly single centre, with a sample size of < 100 (range 31 to 60) participants. The polyclonal IVIG studies on adults were also small, with the exception of three standard IVIG trials (Dominioni 1996; Masaoka 2000; Werdan 2007) and one IgM-enriched immunoglobulin trial (Hentrich 2006) that had a sample size > 100 participants.

Most of the monoclonal trials were relatively large multi-centre studies, except for two anti-endotoxin trials (Greenberg 1992; Lachman 1984) and one anti-cytokine trial (Dhainaut 1995) that had a sample size of < 100 participants.

Excluded studies

We excluded 44 studies for the following reasons:

1. the primary outcome measure was not mortality, in six studies (Christensen 1991; De Groote 1989; Homan 1990; Jones 1995; Kett 1994; Wang 2006);
2. the study was on an animal model (Fischer 1983);
3. the study design was not an RCT (Bojic 1998; Fisher 1993; Freeman 1999; Gunes 2006; Kaul 1999; Okimoto 1985; Panko 1976; Tomii 1985; Ueda 1985; Yavuz 2012; Zeni 1997);
4. the studies were either reviews or meta-analyses (Jenson 1997; Kreymann 2007; Lacy 1995; Laupland 2007; Ohlsson 2013; Soares 2012; Turgeon 2007; Werdan 1996);
5. alternate allocation to treatment and control arms was used (El Nawawy 2005; Gokalp 1994; Marenovic 1998; Sidiropolous 1981);
6. IVIG was the control drug rather than the experimental drug (Cairo 1992; Calandra 1988; Haque 1995; Pilz 1997);
7. the immunoglobulin was administered by the intramuscular route (Aitchison 1985);
8. the study population described was a subgroup of a larger published study (Kornelisse 1997; Wortel 1992);
9. the study participants were patients with specific infections not necessarily sepsis (Jesdinsky 1987);

10. the experimental treatment was a tumour necrosis factor, Fc fusion protein (Fisher 1996; Pittet 1999);
11. the study was an interim analysis (Dominioni 1991) of a clinical trial which we have included in our review (Dominioni 1996); and
12. duplicate publication (Schedel 1996; Sidiropoulos 1986).

Risk of bias in included studies

The assessment of the quality of the individual studies is shown in the table Characteristics of included studies and summarized in Figure 2 and Figure 3.

Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

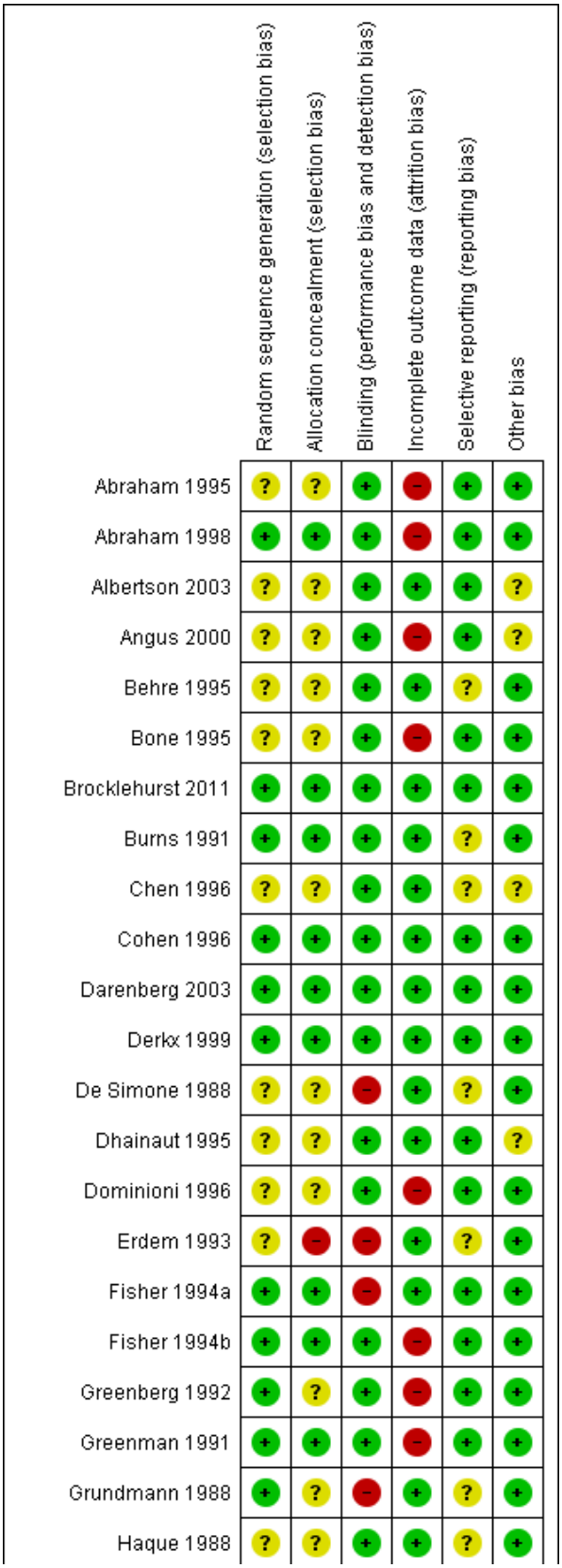


Figure 2. (Continued)

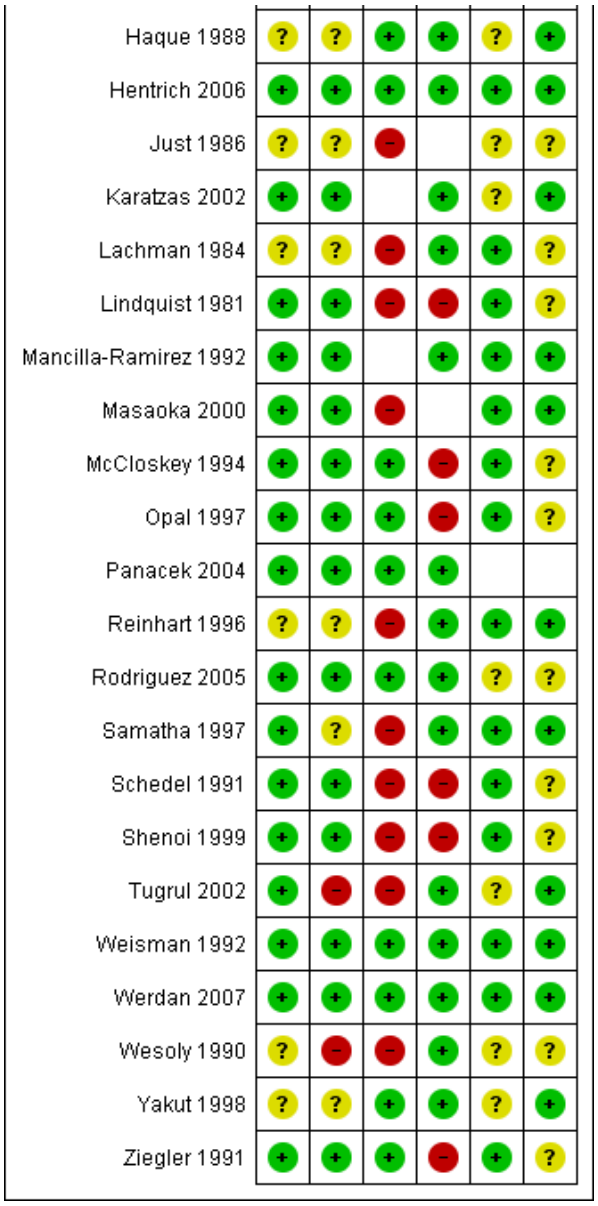
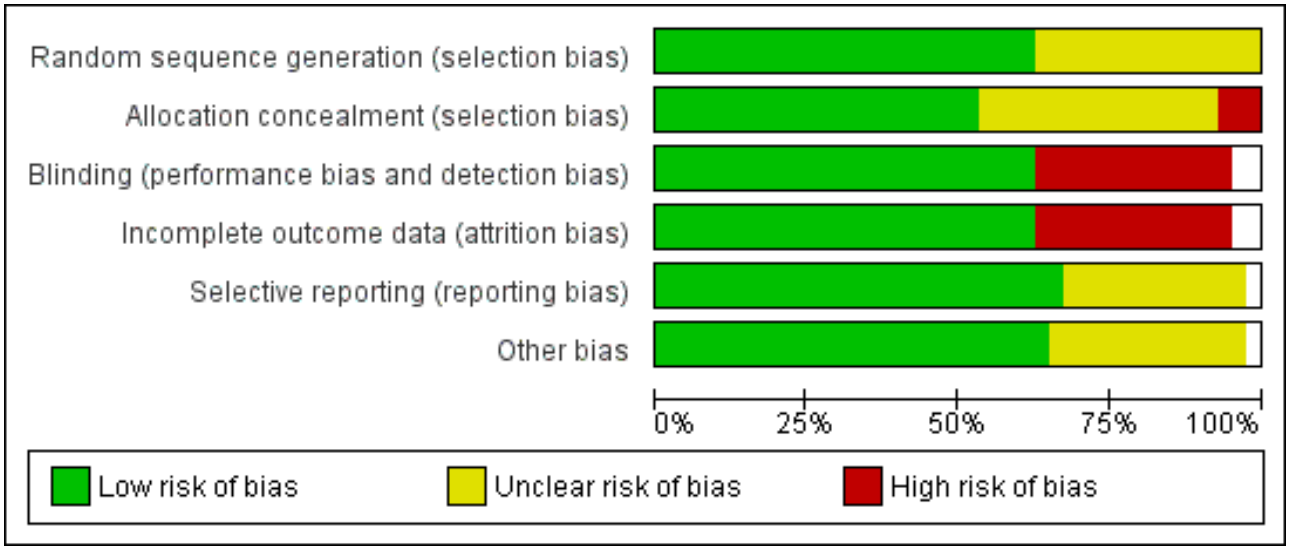


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Polyclonal IVIG trials

Eight trials were assessed as having low risk of bias. That is, they had adequate allocation concealment and blinding with an intention-to-treat analysis. Three of these trials were on polyclonal IVIG in neonates (Brocklehurst 2011; Mancilla-Ramirez 1992; Weisman 1992) and five were in adults (Burns 1991; Darenberg 2003; Hentrich 2006; Rodriguez 2005; Werdan 2007). Of the five trials on adults, three were on medical patients (Burns 1991; Darenberg 2003; Hentrich 2006), one on surgical patients (Rodriguez 2005), and one on mixed medical-surgical patients (Werdan 2007).

Monoclonal trials

Four studies were assessed to have low risk of bias; that is, they had adequate allocation concealment and blinding, with an intention-to-treat analysis. Three were on the anti-cytokines anti-TNF alpha (Abraham 1998; Cohen 1996) and anti-TNF antibody fragment afelimomab (Panacek 2004); and one was an anti-endotoxin trial, specifically HA-1a (Derkx 1999).

Allocation

Of the 17 polyclonal IVIG trials on adults, nine had adequate allocation concealment (Burns 1991; Darenberg 2003; Hentrich 2006; Karatzas 2002; Lindquist 1981; Masaoka 2000; Rodriguez 2005; Schedel 1991; Werdan 2007); two trials had inadequate allocation concealment (Tugrul 2002; Wesoly 1990); and six had unclear allocation concealment (Behre 1995; De Simone 1988; Dominioni 1996; Grundmann 1988; Just 1986; Yakut 1998).

Of the eight polyclonal IVIG trials on neonates, four had adequate allocation concealment (Brocklehurst 2011; Mancilla-Ramirez 1992; Shenoi 1999; Weisman 1992); one trial had a high risk for bias due to inadequate allocation concealment (Erdem 1993); and three had unclear allocation concealment (Chen 1996; Haque 1988; Samatha 1997).

Seven monoclonal trials had unclear allocation concealment (Abraham 1995; Albertson 2003; Bone 1995; Dhainaut 1995; Greenberg 1992; Lachman 1984; Reinhart 1996).

Blinding

Nine polyclonal IVIG trials on adults (De Simone 1988; Grundmann 1988; Just 1986; Karatzas 2002; Lindquist 1981; Masaoka 2000; Schedel 1991; Tugrul 2002; Wesoly 1990) and three trials on neonates (Erdem 1993; Samatha 1997; Shenoi 1999) did not have a placebo in the control group, which precluded blinding.

Two monoclonal trials lacked blinding manoeuvres (Lachman 1984; Reinhart 1996).

Incomplete outcome data

Intention-to-treat analysis was not done in six polyclonal IVIG trials on adults (Behre 1995; Dominioni 1996; Just 1986; Lindquist 1981; Masaoka 2000; Schedel 1991) and one trial on neonates (Shenoi 1999).

Intention-to-treat analysis was not performed in seven monoclonal trials (Abraham 1995; Angus 2000; Bone 1995; Fisher 1994b; Greenman 1991; Opal 1997; Ziegler 1991).

Selective reporting

Only seven (Darenberg 2003; Dominioni 1996; Hentrich 2006; Lindquist 1981; Masaoka 2000; Schedel 1991; Werdan 2007) of the 17 polyclonal IVIG trials in adults and four (Brocklehurst 2011; Samatha 1997; Shenoi 1999; Weisman 1992) of eight trials in neonates included adverse events in their reports.

Other potential sources of bias

Two polyclonal IVIG trials in adults (Just 1986; Wesoly 1990) and one in neonates (Shenoi 1999) had significant differences in the baseline characteristics of the treatment and control groups, which could have influenced the outcome.

Three monoclonal studies were assessed as having a high risk of bias in terms of significant differences in the baseline characteristics of the treatment and control groups that could have influenced the outcome: monoclonal antibody to Enterobacteriaceae (Albertson 2003); anti-TNF alpha (Dhainaut 1995); and anti-LPS (Lachman 1984).

Effects of interventions

See: **Summary of findings for the main comparison** Polyclonal intravenous immunoglobulin (IVIG) versus placebo or no intervention for sepsis, severe sepsis and septic shock; **Summary of findings 2** Polyclonal intravenous immunoglobulin (IVIG) versus placebo or no intervention for sepsis, severe sepsis and septic shock; **Summary of findings 3** Monoclonal antibodies compared to placebo for sepsis, severe sepsis, septic shock; **Summary of findings 4** Monoclonal antibodies compared to placebo for sepsis, severe sepsis, septic shock

All-cause mortality across all IVIG preparations

Forty-three trials fulfilled the inclusion criteria. A pooled analysis of all the IVIG preparations was not done because of clinical heterogeneity.

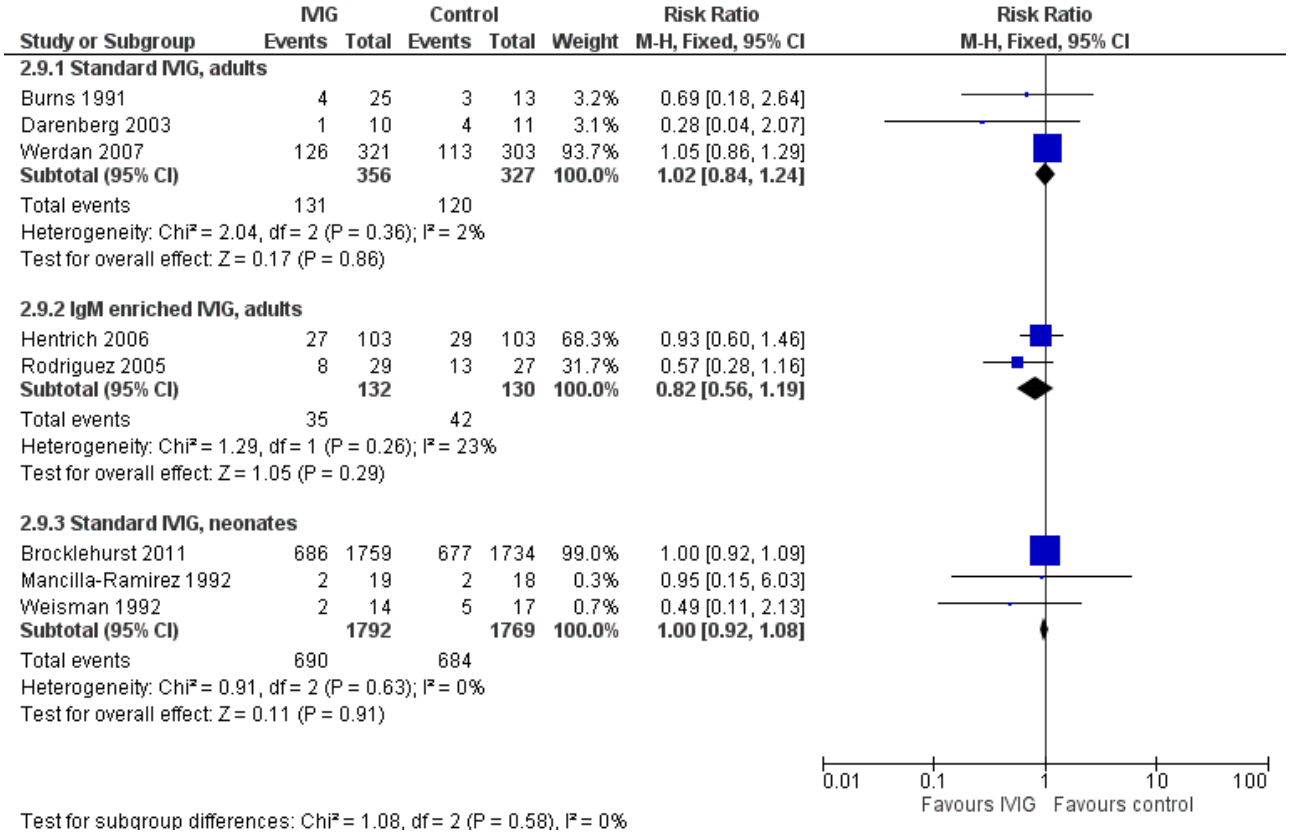
The outcomes were analysed according to the type of IVIG preparation because of the structural differences and the varying mechanisms of action of polyclonal and monoclonal IVIGs, as planned in the protocol.

All-cause mortality by type of immunoglobulin and age group

Polyclonal IVIG in adults

Subgroup analysis of 17 polyclonal IVIG trials in adults with sepsis (n = 1958) demonstrated that polyclonal IVIG significantly reduced short-term mortality (RR 0.77; 95% CI 0.68 to 0.87) but with some degree of heterogeneity across the trials (P = 0.07, I^2 = 36%) (Analysis 2.1). Further subgroup analysis according to type of polyclonal IVIG likewise showed significant reductions in mortality for those participants given standard polyclonal IVIG (RR 0.81; 95% CI 0.70 to 0.93; 10 trials, n = 1430) or IgM-enriched polyclonal IVIG (RR 0.66; 95% CI 0.51 to 0.85; 7 trials, n = 528). The trials of standard polyclonal IVIG had some degree of heterogeneity (P = 0.04, I^2 = 48%) while the trials of IgM-enriched polyclonal IVIG were not heterogenous (P = 0.47, I^2 = 0%). However, sensitivity analysis using the five trials with low risk of bias, three using standard polyclonal IVIG in adults (Burns 1991; Darenberg 2003; Werdan 2007) and two of IgM-enriched IVIG in adults (Hentrich 2006; Rodriguez 2005), did not show a significant reduction in mortality (RR 0.97; 95% CI 0.81 to 1.15; n = 945) (Figure 4; Analysis 2.2). The test for heterogeneity was not significant (P = 0.34, I^2 = 12%).

Figure 4. Polyclonal IVIG versus placebo or no intervention, outcome: all-cause mortality by type of polyclonal IVIG, sensitivity analysis, low risk of bias trials.



The trials that reported long-term mortality, at 60 days (Hentrich 2006) and 180 days (Darenberg 2003), likewise showed no significant reduction in mortality (29.6% versus 34.7%, P = 0.50; 2/10 versus 4/36, respectively).

Meta-analysis using a random-effects model showed significant reduction in mortality (RR 0.70; 95% CI 0.58 to 0.84) (Analysis 1.1) but this reduction was not seen when only trials with low risk of bias were analysed (RR 0.94; 95% CI 0.74 to 1.18) (Analysis 1.2).

Polyclonal IVIG in neonates

Post hoc subanalysis of eight polyclonal IVIG trials in neonates with sepsis showed that polyclonal IVIG did not reduce mortality (RR 0.98; 95% CI 0.91 to 1.07); there was no significant heterogeneity (P = 0.71, I^2 = 0%). Likewise, no significant reduction in mortality was observed with standard polyclonal IVIG (RR 1.00; 95% CI 0.92 to 1.08; n = 3667) or IgM-enriched polyclonal IVIG (RR 0.57; 95% CI 0.31 to 1.04; n = 164) (Analysis 2.3). Sensitivity analysis of three trials on standard IVIG with low risk of bias (Brocklehurst 2011; Mancilla-Ramirez 1992; Weisman 1992) also showed no significant reduction in mortality (RR 1.01; 95% CI 0.93 to 1.09; n = 3561) (Figure 4; Analysis 2.4). Tests for heterogeneity were not significant for both the subgroup and sensitivity analyses.

Random-effects model meta-analysis likewise showed no significant reduction in mortality both for all eight trials on neonatal sepsis (RR 0.99; 95% CI 0.91 to 1.07) (Analysis 1.1) and when only the trials with low risk of bias were analysed (RR 0.81; 95% CI 0.46 to 1.42) (Analysis 1.2).

Monoclonal immunoglobulins - anti-endotoxins

The eight trials of anti-endotoxins (four E5 trials, three HA-1A trials, one anti-LPS trial) were heterogeneous (P = 0.02, I^2 = 57%), precluding an overall estimate of effect (Analysis 3.1). The apparent source of heterogeneity was the HA-1A trial (Ziegler 1991). This trial only analysed patients with confirmed gram-negative bacteraemia and showed a reduction in mortality while the rest of the trials did not show a survival benefit. A sensitivity analysis of one study with low risk of bias (Derkx 1999) and five studies with uncertain risk of bias (Angus 2000; Bone 1995; Greenberg 1992; Greenman 1991; McCloskey 1994) revealed no significant survival benefit (RR 1.01; 95% CI 0.94 to 1.09; n = 4443) (Analysis 3.2). Likewise, a subanalysis of the four trials on E5 monoclonal antibody (Angus 2000; Bone 1995; Greenberg 1992; Greenman 1991) showed no reduction in mortality (RR 0.98; 95% CI 0.88 to 1.10; n = 1975) (Analysis 3.1). Tests for heterogeneity were not significant for both the sensitivity (P = 0.26, I^2 = 23%) and subgroup (P = 0.64, I^2 = 0%) analyses. The three trials of HA-1A antibody (Derkx 1999; McCloskey 1994; Ziegler 1991) were significantly heterogeneous (P = 0.005, I^2 = 81%), which could be due to differences in study population and methodologic quality. The trial of Derkx 1999 involved children with a presumptive diagnosis of meningococcal septic shock; McCloskey 1994 included patients with gram-negative bacteraemia and septic shock; while Ziegler 1991 selectively analysed patients with confirmed gram-negative bacteraemia.

Monoclonal immunoglobulins - anti-cytokines

Pooled analysis of the nine trials on anti-cytokines (six anti-TNF alpha trials, three recombinant human IL-1 receptor antagonist (rh IL-1ra) trials) (Analysis 3.3) revealed a small but significant reduction in mortality (RR 0.92; 95% CI 0.86 to 0.97; n = 7893) with no significant heterogeneity (P = 0.76, I^2 = 0%). Sensitivity analysis of three trials with low risk of bias (Abraham 1998; Cohen 1996; Panacek 2004) and four studies with uncertain risk of bias (Abraham 1995; Fisher 1994a; Fisher 1994b; Opal 1997) showed a marginal reduction in mortality (RR 0.91; 95% CI 0.86 to 0.97; n = 7648) (Analysis 3.4). Likewise, sensitivity analysis of the three studies with low risk of bias (Abraham 1998; Cohen 1996; Panacek 2004) showed a marginal reduction in mortality (RR 0.92; 95% CI 0.86 to 0.99; n = 5065). Tests of heterogeneity were not significant for both sensitivity analyses. It is important to note that the marginal benefit was contributed mainly by one large study (n = 2634) on anti-TNF antibody $F(ab')_2$ fragment afelimomab (Panacek 2004), which showed a marginal reduction in the overall mortality and in the subgroup analysis of patients with elevated IL-6 levels.

Monoclonal antibody for Enterobacteriaceae common antigen

We included one trial on a human monoclonal IgM antibody specific for Enterobacteriaceae common antigen (ECA), which is a specific glycophospholipid surface antigen found in organisms belonging to the Enterobacteriaceae family (Albertson 2003). This trial did not demonstrate reduced mortality in patients with presumed and proven gram-negative sepsis (Analysis 3.5).

Mortality from sepsis

Mortality from sepsis or septic shock was reported in only six trials. A subanalysis of the four adult trials on polyclonal IVIG (Dominioni 1991; Hentrich 2006; Schedel 1991; Yakut 1998) demonstrated a significant decrease in mortality from septic shock (RR 0.45; 95% CI 0.29 to 0.69) (Analysis 2.5). The trials were significantly heterogeneous (P = 0.03, I^2 = 66%) probably due to differences in study population (Analysis 2.5). The largest trial, with a low risk of bias (Hentrich 2006), was conducted on neutropenic patients with haematologic malignancies and did not show any reduction in mortality from sepsis; the small trials on surgical patients (Dominioni 1996; Yakut 1998) and adults with gram-negative septic shock (Schedel 1991) showed reductions in mortality. The monoclonal trial of E5 antibody (Bone 1995) and the polyclonal IVIG trial on neonates (Erdem 1993) did not reduce mortality from sepsis.

Other outcomes

Length of hospital stay among survivors was reported as a secondary outcome measure in 11 polyclonal IVIG trials and one monoclonal IVIG trial (Lachman 1984). A subanalysis of the six polyclonal trials in adults (Dominioni 1996; Grundmann 1988; Just 1986; Lindquist 1981; Tugrul 2002; Wesoly 1990) showed no significant reduction in the length of hospital stay in the IVIG group (MD -3.00; 95% CI -6.37 to 0.38) and there was no significant heterogeneity (Analysis 2.6; subgroup1). These six trials were assessed as having uncertain risk of bias.

Subanalysis of five polyclonal IVIG trials on neonates demonstrated a significant reduction in mortality in the IVIG group (MD -5.84; 95% CI -9.72 to -1.95) but there was moderate heterogeneity (P = 0.11, I^2 = 55%). Sensitivity analysis of trials with low risk of bias (Weisman 1992) and uncertain risk of bias (Chen 1996; Samatha 1997) did not demonstrate any reduction in the duration of hospital stay (Analysis 2.7). The large multi-centre trial on polyclonal IVIG (Brocklehurst 2011) likewise did not show any significant difference in the duration of hospital stay, with a median duration of 64 days (interquartile range 37 to 92 days) in the IVIG group and 64 days (interquartile range 37 to 93 days) in the placebo group.

The bacteriological failure rate was reported in only one polyclonal IVIG trial involving adult medical and surgical patients (De Simone 1988). It showed a significantly higher bacteriological eradication

rate in the IVIG group compared to the control group (40% versus 8%, P < 0.01).

Severity and duration of sepsis were not uniformly defined or stated in the various trials hence no subgroup analyses could be done for these outcomes.

Adverse effects

Only seven polyclonal IVIG trials in adults and four trials in neonates included adverse events in their reports. Of the four trials on neonates, two reported no adverse events attributable to IVIG (Samatha 1997; Shenoi 1999) and one trial (Weisman 1992) reported two suspected infusion-related adverse reactions, specifically hypotension and hypoglycaemia. In the large polyclonal IVIG trial on neonates (Brocklehurst 2011), no significant differences in adverse events were found.

In adults, adverse events reported as likely to be related to polyclonal IVIG were allergic reactions (Hentrich 2006; Werdan 2007); skin reactions such as erythema and exanthem (Hentrich 2006; Werdan 2007); pruritus (Masaoka 2000); nausea and vomiting (Hentrich 2006; Lindquist 1981; Masaoka 2000); dyspnoea (Masaoka 2000); congestion (Werdan 2007); shock (Lindquist 1981); and fever and chills (Lindquist 1981). Two trials reported no adverse events attributable to IVIG (Dominioni 1996; Schedel 1991) and one trial reported adverse events but none that were assessed as related to IVIG (Darenberg 2003).

DISCUSSION

Summary of main results

The use of novel immunotherapeutic agents to combat the intense endotoxin and inflammatory mediator excesses in sepsis has been of major interest in the past decade. This updated meta-analysis conclusively showed that standard polyclonal IVIGs did not decrease mortality among neonates with sepsis, with the inclusion of the large multi-centre high quality trial on polyclonal standard IVIG (Brocklehurst 2011) (Summary of findings for the main comparison). Likewise, among adults with sepsis no reduction in mortality was observed with standard polyclonal IVIG in high quality trials (Summary of findings 2). However, for IgM-enriched polyclonal IVIGs, the evidence of benefit remains insufficient and inconclusive for both adults and neonates with sepsis because of the paucity of large, high quality trials (Figure 5; Figure 6).

Figure 5. Funnel plot of comparison: 2 Polyclonal IVIG versus placebo or no intervention, outcome: 2.1 All-cause mortality, adults, by type of polyclonal IVIG.

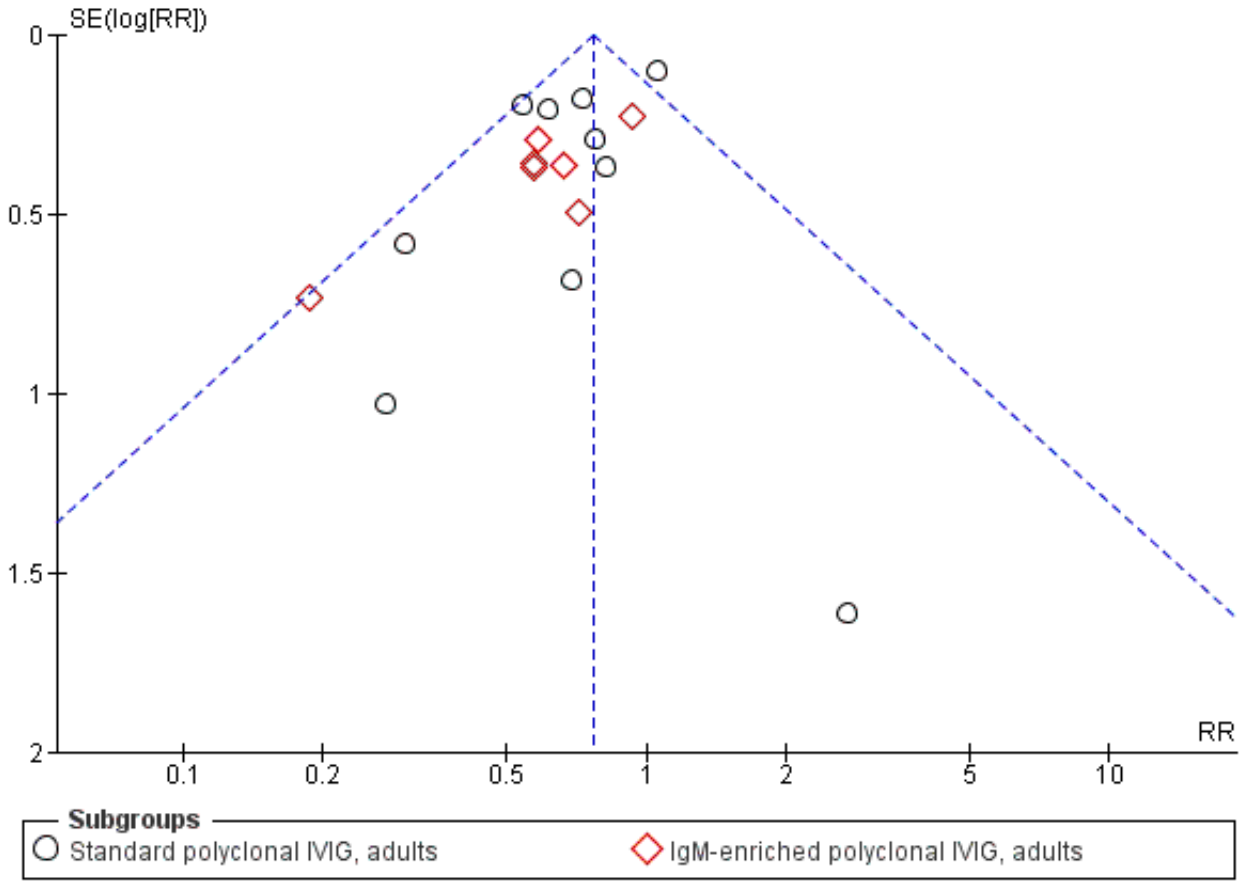
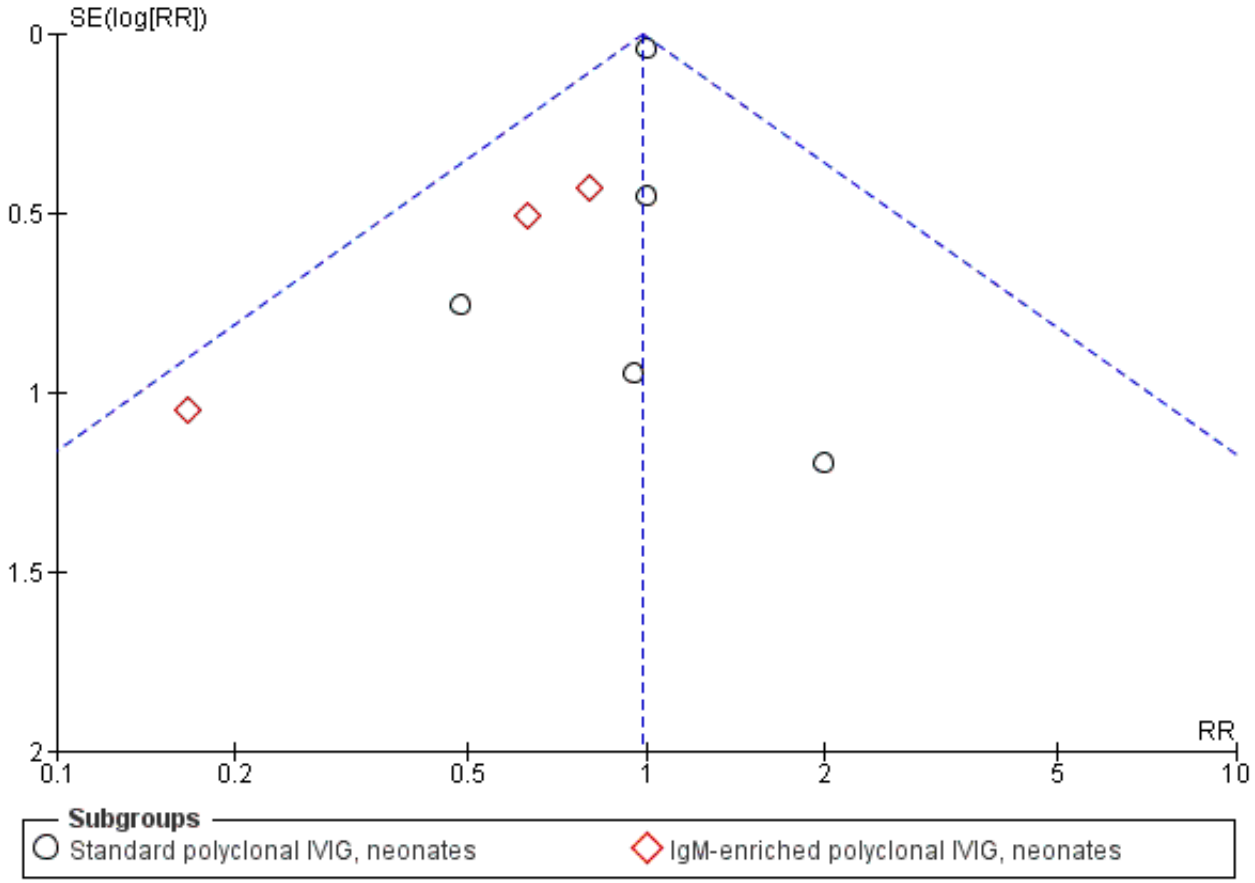


Figure 6. Funnel plot of comparison: 2 Polyclonal IVIG versus placebo or no intervention, outcome: 2.3 All-cause mortality, neonates, by type of polyclonal IVIG.



None of the monoclonal IVIG preparations to date show clinically significant benefit for patients with sepsis. The pooled as well as subgroup analyses of randomized controlled trials of these experimental agents do not demonstrate a significant reduction in mortality among patients with severe sepsis or septic shock. Furthermore, the large trials on E5 (Angus 2000) and anti-TNF alpha (Abraham 1998) failed to demonstrate any significant benefit in the overall mortality analysis and the post hoc subgroup analysis based on presence of shock, co-morbidity, organ failure, site of infection, and type of organism. A trial on human monoclonal IgM antibody that is specific against Enterobacteriaceae likewise did not decrease mortality (Albertson 2003). One large trial on the anti-TNF antibody $F(ab')_2$ fragment afelimomab (Panacek 2004) showed only marginal benefit both in the overall mortality analysis and for the patients with elevated IL-6 levels. See Summary of findings 3; Summary of findings 4.

Overall completeness and applicability of evidence

We have updated our search from 2003 to 2012 and have included all possible trials on polyclonal and monoclonal preparations for adults and neonates with sepsis.

Investigators have postulated that polyclonal IVIG contains immunoglobulin G (IgG) and even IgM (in some preparations), which could boost the immune response of septic patients. Some authors have stressed the potential benefits for immunocompromised patients, such as neonates, who have immunoglobulin and complement deficiencies; and intensive care unit patients, who develop relative immunodepression as a consequence of severe underlying illnesses, surgery, or chemotherapy (Chen 1996; De Simone 1988; Dominioni 1991; Kornelisse 1997; Weisman 1992). In addition, premature infants are significantly compromised because IgG from the mother is transferred to the infant only after the 32nd week of gestation (Chen 1996). Thus, it has been postulated that the administration of immunoglobulin improves the opsonization and phagocytic functions of the neonates' antibodies (Weisman 1992).

Antibacterial activity is reported to be much higher with IgM-enriched preparations compared to the standard IVIG (Haque 1988; Wesoly 1990). The proposed mechanism of action is neutralization of endotoxin in the patient's circulation thus preventing the harmful consequences induced by the lipid-A component of the endotoxin molecule (Schedel 1991).

Another subgroup of septic patients for whom IVIG is proposed to be of likely benefit is those with severe invasive Group A streptococcal infections of varying serotypes. The postulated mechanisms of action include enhancement of bacterial opsonization, complement activation, antigen neutralization, and cytokine modulation resulting in suppression of pro-inflammatory responses (Norrby-Teglund 2003).

It should be noted that there is considerable heterogeneity in the nature and mode of action of the monoclonal antibodies; for example HA-1A and E5 are postulated to act specifically against the lipid-A moiety of the endotoxin, and anti-LPS against the lipopolysaccharide (LPS) molecule of gram-negative bacteria. Likewise, the anti-cytokines act on various inflammatory mediators such as TNF alpha and IL-1 (Dahlberg 1997).

In spite of the differing modes of action and varying potential benefits for different groups of patients, we included the different immunotherapeutic agents in our meta-analyses and performed subgroup analyses. In the actual emergent situation of sepsis and septic shock the clinician opts for these agents without the benefit of laboratory results that might be predictive of a good outcome (for example gram-positive versus gram-negative bacterial aetiology, and levels of specific antibodies or cytokines). More importantly, there is still no validated bedside marker that could aid the physician in identifying specific subgroups of patients that could respond to these immunoadjuvants.

It has been argued by sepsis trialists that perhaps the optimum therapy would be a combination of various immunotherapeutic agents that target different points of the sepsis cascade (Abraham 1994; Bone 1991; Nydegger 1997; Werdan 2001). However, to date there are no randomized controlled trials on such combinations. At this point, adjuvant therapy with monoclonal IVIGs for the treatment of sepsis remains largely experimental, with no robust demonstrable evidence of benefit.

Evidence-based guidelines on sepsis recommend early goal-directed therapy that involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and demand (Dellinger 2008). This is in addition to controlling the source of infection and providing prompt, rational antibiotic use. A randomized controlled trial has shown that early goal-directed resuscitation in the emergency room, for patients presenting with septic shock, significantly improved survival (Rivers 2001).

Other investigators have suggested further improvements in the design of clinical trials on sepsis, for example refining the clinical definition of sepsis, lengthening the duration of observation, and defining other endpoints of benefit (Sibbald 1995). Only a few of the trials included in this review reported long-term mortality, using variable cut-offs ranging from 56 to 180 days. These trials also did not show significant reductions in mortality. A recent systematic review (Annane 2009) suggested six key points for the design and conduct of future sepsis trials, to minimize the sources of heterogeneity.

1. Avoid mixing patients with severe sepsis and with septic shock.
2. Restrict the time window to less than 24 hrs from onset of the first organ dysfunction or shock.
3. Include only definite sepsis.
4. Use the sepsis-related organ failure assessment score for eligibility.
5. Include a first interim analysis after enrolment of 25% of the planned sample size to check the actual baseline risk of death and to recalculate the number of patients needed.
6. Strictly control for concomitant evidence-based interventions as recommended in the 'Surviving Sepsis Campaign' guidelines, such as early goal-directed therapy, source control, and prompt administration of antibiotics (Dellinger 2008; Dellinger 2013).

Potential negative effects from administration of IVIG, such as possible risk of transmission of hepatitis C and prion diseases from poor quality IVIG preparations, have also been pointed out (Erdem 1993; Nydegger 1999). Not all polyclonal studies reported on adverse effects. Of the adverse effects described most were immediate and delayed reactions to the infusion, for example allergic and skin reactions. None of the trials looked at late adverse effects such as transmission of infectious agents.

Quality of the evidence

While this updated meta-analysis provides some evidence of benefit from polyclonal IVIGs in adult patients with sepsis, it should be noted that most of the studies on polyclonal IVIG are small studies, which is in contrast to the 'large', multi-centre studies for monoclonal antibody preparations. Sensitivity analysis of five published trials with low risk of bias (Burns 1991; Darenberg 2003; Hentrich 2006; Rodriguez 2005; Werdan 2007) did not show a reduction in mortality in adults. Hence caution must be taken in the interpretation of statistically significant results from the pooled analysis of small studies (Cappelleri 1995; Villar 1995), particularly those with poor methodologic quality. For instance, some of the small studies were noted to have methodologic flaws. Wortel in a letter to the editor (Wortel 1993) noted some methodological deficiencies, such as multiple interim analyses, in one of the studies showing a significant reduction in mortality (Schedel 1991).

For the meta-analysis of polyclonal IVIG trials on adults, there was evidence of significant funnel plot asymmetry (Figure 5) when using Egger's statistic (bias -1.3, P = 0.01) but not when using the Begg-Mazumdar statistic (Kendall's tau -0.07, P = 0.66). While publication bias may partly explain the asymmetry, it is likely that the poor methodologic quality of the small studies is also contributing to the asymmetry. As stated above, the sensitivity analysis of studies with low risk of bias showed no reduction in mortality for both adults and neonates. Thus small study effects and poor methodologic quality are likely to contribute to the lack of robustness of the observed reduction in mortality seen in the pooled analysis of all the studies. It is also of note that, except for one trial (Burns 1991), the high quality polyclonal IVIG trials in adults (Darenberg 2003; Hentrich 2006; Rodriguez 2005; Werdan 2007) were all published after the year 2000, after the first version of our review (Alejandria 2000). This updated review confirms the lack of robust strong evidence on the effectiveness of IVIG in reducing mortality among patients with sepsis.

Agreements and disagreements with other studies or reviews

The addition of the large trial on standard polyclonal IVIG (Brocklehurst 2011) to our meta-analysis of polyclonal IVIG for neonatal sepsis conclusively showed no benefit in reducing mortality, in contrast to a previous meta-analysis (Jenson 1997). A comparison of the studies that were included in our meta-analysis and those in Jenson et al showed that the latter review did not include thee trials that had no significant reduction in mortality among neonates (Brocklehurst 2011; Chen 1996; Erdem 1993); in addition, we excluded a study by Sidiropolous (Sidiropolous 1981) which used alternate allocation of the interventions. Our meta-analysis is in agreement with another Cochrane review

(Ohlsson 2013), which focused on polyclonal IVIG for suspected or subsequently proven infection in neonates and analysed a similar set of studies. Ohlsson et al concluded that the evidence is insufficient to support the routine administration of IVIG to prevent mortality in infants with suspected or proven neonatal infection. Another meta-analysis (Kreymann 2007), which included more trials, showed significant reductions in mortality for both standard (RR 0.63; 95% CI 0.42 to 0.96; 7 trials, n = 358) and IgM-enriched polyclonal IVIG trials (RR 0.50; 95% CI 0.34 to 0.73; 5 trials, n = 352). However, the additional trials in this meta-analysis were also of small sample size and either used alternate allocation (El Nawawy 2005; Gokalp 1994; Sidiropolous 1981) or had unclear allocation concealment (Gunes 2006), which could have led to an overestimate of the treatment effects. The completion of the large polyclonal IVIG trial on neonates has provided definitive high quality evidence that standard polyclonal IVIG does not effectively reduce mortality among neonates with sepsis (Brocklehurst 2011). One small study from Turkey on polyclonal IVIG in 60 neonates with blood culture confirmed sepsis that is awaiting quality assessment is unlikely to change the conclusions (Yildizdas 2005).

In contrast to the meta-analysis on neonatal sepsis, the meta-analysis on adult patients showed a significant reduction in mortality with the use of polyclonal IVIG. The results of our meta-analysis of 17 trials is consistent with the results of three meta-analyses on polyclonal IVIG for adults with sepsis (Kreymann 2007; Laupland 2007; Turgeon 2007), which all showed a survival benefit among patients who received polyclonal IVIG despite the variations in the number of trials included. Additionally, our subgroup analysis by type of polyclonal IVIG is in agreement with the subanalysis by Kreymann (Kreymann 2007), which also showed reductions in mortality for both standard IVIG and IgM-enriched polyclonal immunoglobulin. On the other hand, the meta-analysis of Pildal and Goetzsche (Pildal 2004) showed no reduction in mortality in a sensitivity analysis of two high quality trials in adults (Burns 1991; Darenberg 2003); one in neonates (Mancilla-Ramirez 1992); and another trial that was an unpublished study (Werdan 1997 abstract). While we included the same trials, we also subanalysed the trials into adults and neonates. Our sensitivity analysis of high quality trials in adults, which includes a large study on polyclonal IVIG that was published 10 years after its completion (Werdan 2007) plus two studies published after 2004 (Hentrich 2006; Rodriguez 2005), also showed no reduction in mortality. The sensitivity analysis according to methodologic quality likewise demonstrated a lack of robustness of the survival benefit that was initially seen when all the trials were pooled.

Another meta-analysis included in a recent health technology assessment report (Soares 2012), which simultaneously analysed the type of IVIG, dosing regimen and quality indicators, reached similar conclusions as our review despite some variations in the assessment and interpretation of quality and in the studies included and excluded. The modelling process identified trial quality, publication bias, small study effects and dosing regimen as factors contributing to the heterogeneity of the treatment effects of IVIG. Value of information analysis and a cost-effectiveness decision model identified uncertainties in the mechanism of action of IVIG, dose and duration of IVIG therapy, and the heterogenous nature of severe sepsis as important issues that need to be addressed in future reviews and basic research. This information is needed to inform the design of a definitive RCT and re-evaluate its impact on the expected value of the information before investing resources on such potentially costly research.

AUTHORS' CONCLUSIONS

Implications for practice

Intravenously administered polyclonal immunoglobulins, particularly standard polyclonal IVIG, do not provide benefit as adjuvant therapy in sepsis in terms of reducing mortality among neonates and adults with sepsis. Likewise, intravenous monoclonal immunoglobulins do not show clinically significant survival benefits. There is no good evidence that a combination of immunotherapeutic agents that target different mediators in the sepsis cascade is effective.

Implications for research

Large, multi-centre studies are needed to confirm the effectiveness of IgM-enriched polyclonal immunoglobulins in reducing mortality in adults. The current evidence for benefit is inconsistent and inconclusive. Among adults, septic patients other than surgical patients could be included in future trials. Further studies are also needed on the subgroup of patients with necrotizing fasciitis and streptococcal toxic shock syndrome (STSS) to provide evidence on clinical efficacy of IVIG in STSS. This is especially important because the European RCT on STSS was prematurely terminated (Darenberg 2003), and yet IVIG continues to be recommended as a promising adjuvant in STSS and necrotizing fasciitis. In addition, future trials should include the sepsis bundle of evidence-based interventions as the standard of care, for example early goal-directed therapy for severe sepsis and septic shock and antibiotic administration within one hour (Dellinger 2008; Dellinger 2013), to determine whether the addition of IVIG to the sepsis bundle of care would contribute to a further reduction in mortality.

In summary, the design of future trials might be improved by the following:

1. refining the clinical definition of sepsis and including only patients with definite sepsis, using standardized scoring systems, e.g. Sequential Organ Failure Assessment;
2. stratifying patients to address intrinsic differences in the patient population and the severity of sepsis;
3. adding endpoints besides the measurement of all-cause mortality, such as the resolution or reversal of organ failure;
4. lengthening the duration of observation and follow up;
5. systematic reporting of adverse events; and
6. instituting the sepsis bundle of care as the standard intervention in the control group.

A recent health technology assessment report, however, argues that basic research on the mechanism of action of IVIG in severe sepsis should be reviewed and be done to appropriately guide the design of a future multi-centre RCT rather than immediately embarking on a large RCT on the clinical effectiveness of IVIG (Soares 2012).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abraham 1995

Methods	RCT, multi-centre
Participants	Adult patients with sepsis or septic shock ,18 years of age or older 31 hospitals in USA and Canada
Interventions	TNF alpha MAb (single infusion of 15 mg/kg or 7.5 mg/kg) versus placebo (2.5 g/L human albumin)
Outcomes	28-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated

Abraham 1995 *(Continued)*

Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled (human albumin)
Incomplete outcome data (attrition bias) All outcomes	High risk	intention-to-treat analysis not done
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Abraham 1998

Methods	Randomized, multi-centre
Participants	Adults > 18 years old with septic shock of 12 hours or less duration 105 hospitals in USA and Canada
Interventions	TNF alpha MAb 7.5 mg/kg single infusion versus placebo (0.25% human serum albumin)
Outcomes	28-day all-cause mortality, 7-day and 14-day all-cause mortality Reversal of septic shock at day 7 Resolution of baseline organ failure at day 7
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized blocks of eight kits
Allocation concealment (selection bias)	Low risk	Computer-generated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled (human serum albumin)
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Albertson 2003

Methods	Randomized, multi-centre
Participants	Adult patients, 18 years or older, with sepsis from presumed or proven gram-negative infection in 33 US medical centres
Interventions	300 mg MAB-T88 in albumin IV single dose versus placebo (human serum albumin in an equivalent volume)
Outcomes	28-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled (human serum albumin), blinded clinical evaluation committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Higher percentage of chronic renal failure in the MAB-T88 group (5.6% versus 3.1%) and shock in the placebo group (85.8% versus 80.3%), but the number of patients requiring vasopressors was equal (49.2% versus 48.4%)

Angus 2000

Methods	Randomized, multi-centre -136 medical centres in the USA
Participants	Adults 18 years or older with severe sepsis and documented or probable gram-negative infection, from April 1993-97
Interventions	E5 2mg/kg/day, 2 doses by IV infusion 24 hrs apart versus placebo consisting of 0.1 mg/ml human serum albumin
Outcomes	14-day and 28-day mortality, adverse event rates, 14-day and 28-day mortality in the subgroup without shock at presentation
Notes	2 planned interim analyses

Risk of bias

Bias	Authors' judgement	Support for judgement

Angus 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Patients were entered into the study only after review and approval of entry criteria by a screening authorization committee on call 24 hours a day"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, identical in appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients lost to follow up and with missing data were included in the denominator
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	2 planned interim analyses

Behre 1995

Methods	Randomized controlled trial, single centre
Participants	Adults with haematologic malignancies, neutropenia and sepsis syndrome or septic shock in Germany Aug 1992 to Sept 1994
Interventions	IgM-enriched Ig (Pentaglobin) loading dose of 0.2 l, then 0.1 l every 6 hrs for 72 hrs as slow IV infusion for a total dose of 1.3 litres versus 5% human albumin
Outcomes	28-day all-cause mortality Endotoxin plasma concentrations IgM and IgG antibodies against lipid-A and re LPS
Notes	Adverse effects not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, 5% human albumin
Incomplete outcome data (attrition bias) All outcomes	Low risk	Interim analysis; no dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse effects not reported

Behre 1995 *(Continued)*

Other bias	Low risk

Bone 1995

Methods	RCT, multi-centre
Participants	Adults with: 1. known or suspected gram-negative infection 2. clinical evidence of sepsis 3. signs of end-organ dysfunction 53 hospitals in USA from Feb 1989 - Jan 1991
Interventions	E5 2 mg/kg/day, 2 doses 24 hrs apart versus placebo (0.1 mg human albumin/ml of buffer solution used for E5)
Outcomes	30-day all-cause mortality Resolution and prevention of organ failure Proportion discharged from the hospital
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Identical placebo, persons administering therapy were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Brocklehurst 2011

Methods	Randomized, placebo-controlled
Participants	Infants receiving antibiotics with clinical evidence of definite or highly probable sepsis and there is substantial uncertainty that IVIG is indicated and birthweight is < 1500 g or infant already has positive blood culture or infant is receiving artificial ventilation

Brocklehurst 2011 *(Continued)*

	3493 infants from 113 hospitals (UK, Australia, Argentina, New Zealand, Serbia, Greece, Denmark, Belgium, Ireland)
Interventions	500 mg/kg (10ml/kg) of IVIG or identical colourless placebo (0.2% albumin solution in normal saline) infused over 4 to 6 hrs, repeated 48 hrs later
Outcomes	Primary: mortality or major disability, at 2 yrs corrected for gestational age Secondary: mortality, chronic lung disease or major cerebral abnormality before hospital discharge Health service utilization: length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment sequence was generated by the National Perinatal Epidemiology Unit in Oxford, UK with balance within random block sizes of 2 to 8; in Australia and New Zealand, randomization list was generated by the National Health and Medical Research Council Clinical Trials Centre in Sydney
Allocation concealment (selection bias)	Low risk	Infants were randomized in blinded fashion. In Europe and Argentina, neonatal staff opened the next sequentially numbered pack, which was stored in the neonatal unit. In Australia and New Zealand, hospital pharmacy was contacted for the assignment.
Blinding (performance bias and detection bias) Mortality	Low risk	Identical placebo and IVIG prepared separately by pharmacists; syringes and tubing were masked with yellow tape
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Burns 1991

Methods	RCT
Participants	Adults with documented sepsis and thrombocytopenia related directly to the infection; patients were in the medical and surgical ICUs New York
Interventions	IVIG (Sandoglobulin) 400 mg/kg/day for 3 days versus albumin
Outcomes	Main outcome measure of the study was an increase in platelet count by day 9 of the study Secondary outcome - mortality
Notes	Five patients had clinically significant bleeding (four in the placebo group)

Risk of bias

Burns 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Sealed, opaque and sequentially numbered envelopes, based on the review of Pildal and Goetzsche (Pildal 2004) who communicated with Burns
Blinding (performance bias and detection bias) Mortality	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 patients completed the full 9 days of follow up
Selective reporting (reporting bias)	Unclear risk	Adverse events related to IVIG were not reported
Other bias	Low risk	

Chen 1996

Methods	RCT, single centre
Participants	Neonates (full-term and premature newborns) with sepsis and bacteraemia 1 hospital in Taiwan; Jan 1993 - April 1995
Interventions	Standard IVIG (Intraglobin) 500 mg/kg 2 hr single infusion versus 0.9% sodium chloride placebo
Outcomes	All-cause mortality with weekly follow up for 6 weeks after discharge Duration of hospitalisation
Notes	Adverse effects were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly divided into 2 groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up; no dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse effects not reported

Chen 1996 *(Continued)*

Other bias	Unclear risk	Patients with negative blood cultures were excluded from the study

Cohen 1996

Methods	RCT, multi-centre, international
Participants	Adult patients with sepsis or septic shock 40 hospitals in 14 countries from May 1991 - July 1993 (England, France, Germany, Sweden, Norway, Belgium, Austria, Italy, Switzerland, Netherlands, Spain, Israel, South Africa, Greece
Interventions	Anti-TNF alpha (15 mg/kg or 3 mg/kg as single infusion) versus placebo (0.25% human albumin)
Outcomes	28-day all-cause mortality Shock reversal and frequency of organ failure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Pharmacist was the only individual aware of treatment allocation
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled; independent safety and efficacy committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Darenberg 2003

Methods	RCT
Participants	Adult patients 18 years and above with streptococcal toxic shock syndrome 17 hospitals in Sweden, Norway, Finland and The Netherlands Jan 1999 - May 2001
Interventions	IVIG (Endobulin S/D; Baxter) at 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3 versus 1% albumin
Outcomes	28-day mortality, mortality at day 180 Time to resolution of shock

Darenberg 2003 *(Continued)*

Notes	Trial was terminated prematurely due to slow patient recruitment Adverse events were reported but none were assessed to be related to the study drug

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Centralized randomization based on the review of Pildal and Goetzsche (Pildal 2004) who communicated with Norrby-Teglund for Darenberg
Blinding (performance bias and detection bias) Mortality	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

De Simone 1988

Methods	RCT, single centre
Participants	Adults with severe sepsis (gram-positive and gram-negative) and septic shock (14 underwent surgery, 5 with neoplasia, 2 with trauma) ICU in Milan, Italy from Jan 1984 - March 1985
Interventions	Standard IVIG (Sandoglobin) slow infusion 0.4 g/kg on day of admission, 0.2 g/kg after 48 hrs and 0.4 g/kg as needed clinically plus antibiotics versus antibiotics alone
Outcomes	All-cause mortality Mortality from septic shock Bacteriologic failure rate
Notes	Adverse effects not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes

De Simone 1988 *(Continued)*

		Assessed as unclear allocation concealment by Pildal and Goetzsche (Pildal 2004); sealed envelopes but unknown whether opaque and sequentially numbered
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Derkx 1999

Methods	Randomized, multi-centre
Participants	Children with ages >3 months to <18 years old with presumptive diagnosis of meningococcal septic shock April 1991 - May 1995 26 paediatric ICUs in the Netherlands, Great Britain, France, Spain, Norway
Interventions	HA-1A 5 mg/kg BW IV single dose versus placebo (3.5 g serum albumin)
Outcomes	28-day and 56-day all-cause mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Independent co-ordinating centre created a treatment allocation code. Full randomization codes remained concealed until completion of the primary analysis
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled; independent safety and efficacy monitoring committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Dhainaut 1995

Methods	RCT, multi-centre
Participants	Adult patients with septic shock within a 12-hour period 7 ICUs in France (5) and Belgium (2) from Sept 1992 - May 1993
Interventions	Anti-TNF alpha (single dose of either 0.1, 0.3, 1.0 or 3.0 mg/kg) versus placebo
Outcomes	28-day all-cause mortality Cytokine and TNF alpha concentrations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned to receive either placebo of one of 4 dosage regimens
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, blinded clinical evaluation committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Placebo group had a higher mean age and more patients with non-fatal underlying disease

Dominioni 1996

Methods	RCT, multi-centre
Participants	Surgical patients with sepsis scores of 17 or greater, 15-80 years old ICUs of Italy, 1986-94
Interventions	Polyclonal IgG given at 0.4g/kg on days 0, 1 then 0.2g/kg on day 5 versus human albumin in 5% dextrose water
Outcomes	All-cause mortality Mortality from septic shock, multiorgan failure Duration of ICU stay of survivors and non-survivors
Notes	No adverse events attributable to IVIG

Risk of bias

Dominioni 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were prospectively randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysis was not intention to treat but ITT data could be derived (4 patients died - 2 IVIG treated, 2 control)
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Erdem 1993

Methods	Quasi-randomized, single centre - Turkey
Participants	Pre-term infants 31-37 weeks with neonatal sepsis diagnosed by Tollner's Sepsis Scoring System
Interventions	IgM-enriched IVIG (Pentaglobin) 5ml/kg/d for 3 days versus no intervention
Outcomes	Mortality from sepsis
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Allocation concealment not stated. Based on the communication of Ohlsson and Lacy (Ohlsson 2013) with Erdem, allocation was performed on an "alternating basis"
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up; no dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported

Erdem 1993 *(Continued)*

Other bias	Low risk

Fisher 1994a

Methods	Randomized, multi-centre
Participants	Adult patients with sepsis syndrome 18 years old and above 12 academic medical centre ICUs in USA
Interventions	Human interleukin-1 receptor antagonist (rhIL-1ra) 100 mg loading dose followed by 72-hr IV infusion of either 1 of 3 doses of 17, 67, or 133 mg/hr versus placebo
Outcomes	28-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent co-ordinating centre prepared the randomization code
Allocation concealment (selection bias)	Low risk	Treatment assigned by a telephone randomization system
Blinding (performance bias and detection bias) Mortality	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Fisher 1994b

Methods	RCT, multi-centre, multi-national
Participants	Adult patients with sepsis or septic shock 63 academic medical centres in USA, Canada and Europe
Interventions	Human IL-1 receptor antagonist (rhIL-1ra) 100 mg loading dose followed by 8 hr infusion of either 1or 2 mg/kg/hr dosage regimens versus placebo
Outcomes	28-day all-cause mortality Survival time in patients with organ dysfunction

Fisher 1994b *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Central, computerized telephone randomization system
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, independent safety and efficacy monitoring committee
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Greenberg 1992

Methods	RCT, single centre
Participants	Adult patients with gram-negative infections Surgical, neurosurgical, medical ICUs in a multi-disciplinary university hospital, United States September 1986 - June 1988
Interventions	E5 (2.5 and 7.5 mg/kg, given as 2 infusions 24 hrs. apart) versus placebo (5% dextrose in normal saline solution)
Outcomes	21-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization code
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled; all participating individuals except the pharmacist and statistician were blinded to the treatment patients received

Greenberg 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT data can be derived
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Greenman 1991

Methods	RCT, multi-centre
Participants	Adults >18 years of age with signs of gram-negative infection and a systemic septic response 33 university-affiliated centres, community and municipal hospitals in USA February 1987 - June 1988
Interventions	E5 2 mg/kg/day, 2 doses 24 hrs apart versus placebo (5% dextrose in normal saline)
Outcomes	30-day all-cause mortality Resolution of organ failure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Code was known only to the pharmacist and statistician
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Grundmann 1988

Methods	RCT, single centre
Participants	Adults with post-operative gram-negative sepsis and endotoxaemia, 11-73 years old Surgical intensive care unit in Germany over 18 months

Grundmann 1988 *(Continued)*

Interventions	Standard IVIG (Intraglobin) 0.25 g/kg on day of study entry and the following day versus no intervention
Outcomes	All-cause mortality Duration of intensive care
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random list was prepared by a computer
Allocation concealment (selection bias)	Unclear risk	Randomized envelope technique Assessed as unclear allocation concealment by Pildal and Goetzsche (randomized envelope technique but unknown whether envelopes were opaque and sequentially numbered) (Pildal 2004)
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Haque 1988

Methods	RCT
Participants	Neonates with first episode of sepsis Maternity and Children's Hospital in Riyadh, Saudi Arabia for 6 months
Interventions	Standard IVIG (IgM enriched) 500 mg/kg single infusion for 2 hrs versus 10% dextrose placebo
Outcomes	All-cause mortality
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Sealed envelope, unclear if opaque and sequentially numbered

Haque 1988 *(Continued)*

Blinding (performance bias and detection bias) Mortality	Low risk	IVIG and dextrose were dispensed in similar, unmarked bottles. The physician treating the infants was not aware of the contents. Assessed as non-blind by Pildal and Goetzsche (Pildal 2004); pentaglobin is opaque while dextrose is not; no precautions to conceal this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up; no dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Hentrich 2006

Methods	RCT, multi-centre
Participants	Neutropenic patients with hematologic malignancies and sepsis syndrome or septic shock age ≥ 18 years old 6 university hospitals in Germany July 1992 to December 1999
Interventions	1300 ml of IV IGMA (Pentaglobin, Biotest Pharma GmbH) infused within 72 hrs given as follows: 200 ml initially (0.5 ml/min) followed by 11 infusions 100 ml each given every 6 hrs versus 1300 ml of 5% human albumin given according to the same schedule as iv IGMA
Outcomes	28 and 60-day all-cause mortality Sepsis-related 28-day mortality, mortality from septic shock
Notes	5 adverse events likely related to IVIG (2 Grade 4 allergic events, 1 Grade 1 allergic reaction, 1 Grade 1 erythema, 1 Grade 2 nausea and vomiting

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list stratified by sepsis syndrome versus septic shock by an independent statistician
Allocation concealment (selection bias)	Low risk	Sealed envelopes with a unique patient number
Blinding (performance bias and detection bias) Mortality	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Just 1986

Methods	RCT
Participants	Intensive care patients >15 years old with severe infections Germany, 65 out of 104 patients had surgery June 1979 - July 1982
Interventions	IVIG 100 ml given at 0h, 12h, 24h and 36h combined with antibiotics versus antibiotics alone
Outcomes	Mortality Duration of intensive care
Notes	Bias: there were more patients in the IVIG group with post-operative complications Only the 29 patients with definite sepsis out of 104 ICU patients were included in this meta-analysis Adverse effects not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unspecified simple randomized allocation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	High risk	
Selective reporting (reporting bias)	Unclear risk	Only the 29 patients with definite sepsis out of 104 ICU patients were included in this meta-analysis Adverse effects not reported
Other bias	Unclear risk	There were more patients in the IVIG group with post-operative complications

Karatzas 2002

Methods	RCT
Participants	Adult patients with severe sepsis in Greece
Interventions	IgM enriched IVIG
Outcomes	28-day mortality
Notes	Adequate allocation concealment based on communication of Pildal and Goetzsche (2004) with Karatzas Adverse events not reported

Risk of bias

Karatzas 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Computer-generated randomization sequence kept centralized apart from clinical centre
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Lachman 1984

Methods	RCT, single centre
Participants	Obstetric and gynaecological patients with septic shock Referral teaching hospital in South Africa from January 1 1983 to January 31 1984
Interventions	Anti-LPS IgG 2 units rapid infusion followed by continuous slow infusion at 1 unit/hr; booster doses as needed for complications versus normal freeze-dried plasma
Outcomes	All-cause mortality Duration of hospital stay
Notes	Small sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated to 2 groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	There were more septic abortions and surgical interventions in the control group

Lindquist 1981

Methods	RCT, single centre
Participants	Adult patients >18 years old with suspected or confirmed septicaemia
Interventions	Pepsin-treated Gamma-Venin 0.15 g/kg infused over 1 hr repeated after 24 and 48 hr and once weekly throughout the antibiotic therapy versus no treatment
Outcomes	Mortality Duration of hospital stay
Notes	Adequate allocation concealment based on communication of Pildal and Goetzsche (2004) with Lindquist. Adverse reactions in the IVIG group: shock (2 patients), rigor, chills and elevation of temperature (5 patients), vomiting (1 patient), rigours, chills and somnolence (1 patient)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Sealed, opaque, sequentially numbered envelopes
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Critically ill patients unable to give informed consent were excluded

Mancilla-Ramirez 1992

Methods	Randomized, single centre
Participants	Neonates (full-term and near-term) with confirmed septicaemia
Interventions	IVIG 500 mg/kg single dose versus 10% maltose
Outcomes	Mortality Serum IgG levels Duration of hospital stay
Notes	Data obtained from abstract of the article and Cochrane review of Ohlsson and Lacy (Ohlsson 2013) pending retrieval of the full text of the article

Mancilla-Ramirez 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Sealed, opaque sequentially-numbered envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Masaoka 2000

Methods	Randomized, multi-centre
Participants	Patients with sepsis or suspected sepsis, severe infections not responding to broad spectrum antibiotics. 141 centres in Japan, 16 to 70 years
Interventions	Standard IViG 5 g daily for 3 days
Outcomes	Defervescence and eradication of symptoms by day 7
Notes	Data on mortality was obtained through communication with Dr Masaoka Adverse effects reported to be probably related to IVIG were nausea and vomiting (2), pruritus (1) and dyspnoea (1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Participants were registered with central committee and allocated by telephone or fax
Blinding (performance bias and detection bias) Mortality	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

McCloskey 1994

Methods	RCT, multi-centre
Participants	Adult patients >18 years of age with gram-negative bacteraemia and septic shock 513 community and university-affiliated hospitals in USA
Interventions	HA-1A 100 mg single infusion versus placebo
Outcomes	14-day all-cause mortality rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Independent randomization centre prepared the treatment allocation schedule. The randomization centre labelled the study material with sequential vial numbers according to the allocation schedule
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT data available
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Baseline characteristics of treatment and control group not given Trial stopped at the first interim analysis

Opal 1997

Methods	RCT, multi-centre
Participants	Adults with severe sepsis or septic shock 91 academic medical centres, intensive care units in North America and Europe
Interventions	rhIL-1ra 100 mg IV bolus followed by 72-hr continuous IV infusion at 2.0 mg/kg/hr versus placebo
Outcomes	28-day all-cause mortality rate resolution of sepsis-specific organ dysfunction
Notes	No significant difference in adverse events

Risk of bias

Opal 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization process
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Mortality	Low risk	Identically packaged placebo, blinded clinical evaluation committee
Incomplete outcome data (attrition bias) All outcomes	High risk	906 patients were enrolled at the time the study was terminated, complete information was available only for 696 patients
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	There were more patients with DIC in the placebo group but subgroup analysis showed no significant difference in mortality rate. Interim analysis was done after about half of the target population had completed the trial. The study was terminated by the sponsor after the Safety and Efficacy Monitoring Board determined that the likelihood of reaching a statistically significant difference in outcome for the primary objective was low.

Panacek 2004

Methods	Randomized, multi-centre
Participants	2634 patients 18 years or older with severe sepsis secondary to documented infection, of whom 998 had elevated IL-6 levels
Interventions	Afelimomab (Fab'$_2$ fragment of a murine monoclonal antibody to human TNFα) 1mg/kg versus placebo for 3 days
Outcomes	28-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Computer-generated sequence; randomization and assignment took place in the pharmacy
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled

Panacek 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk

Reinhart 1996

Methods	RCT, multi-centre, multi-national
Participants	Adults with severe sepsis or septic shock 16 academic medical centres' intensive care units in 6 European countries (Germany, England, Switzerland, Spain, Austria, France)
Interventions	Anti-TNF (0.1, 0.3 or 1.0 mg/kg given in 9 doses at 8-hr intervals over 3 days) versus placebo
Outcomes	28-day mortality Cytokine concentrations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Mortality	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Rodriguez 2005

Methods	RCT, multi-centre
Participants	Adults with severe sepsis and septic shock of intra-abdominal origin admitted to the ICU within 24 hrs after the onset of symptoms, post-surgery 7 teaching hospitals in Spain and Argentina
Interventions	IgM-enriched polyvalent immunoglobulin 7 ml/kg/day for 5 days versus 5% human albumin
Outcomes	30-day all-cause mortality

Rodriguez 2005 *(Continued)*

	Duration of ICU stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list stratified by centre
Allocation concealment (selection bias)	Low risk	Central randomization process (contact by telephone to a central office)
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse effects were not reported
Other bias	Unclear risk	After blind interim analysis of the data from 56 patients, enrolment was stopped because a significant difference in mortality rate in a subgroup analysis of evaluable patients with appropriate antibiotic therapy was documented

Samatha 1997

Methods	Randomized, single centre - Bangalore, India
Participants	Neonates with sepsis Jan 1993 to Dec 1993 in the neonatal ICU
Interventions	IgM-enriched immunoglobulin (Pentaglobin) 5 ml/kg/d as single dose infused at 1.7 ml/kg/hr for 3 consecutive days versus supportive treatment and antibiotics
Outcomes	All-cause mortality Duration of hospital stay, survivors
Notes	No complications attributable to IVIG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned by picking up lots
Allocation concealment (selection bias)	Unclear risk	Not stated

Samatha 1997 *(Continued)*

Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up; no dropouts
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Schedel 1991

Methods	RCT, single centre
Participants	Adults with gram-negative septic shock within 24 hours after the onset of symptoms (7-73 years old) Clinical immunology ward in a university hospital in Germany, 33 months study period
Interventions	Standard IVIG (Pentaglobin) 600 ml as an 8 hr infusion then 300 ml on days 2 & 3 in the period 24 hrs after the previous dose versus no intervention
Outcomes	6-week all-cause mortality Mortality from sepsis
Notes	Multiple interim analyses No side effects observed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 14 patients excluded from the final analysis, 7 patients received IVIG and no patient died. in the group of 7 patients who did not receive IVIG, 2 died
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Multiple interim analyses

Shenoi 1999

Methods	RCT, multi-centre
Participants	Neonates with probable sepsis and birthweight of more than 1000 g 3 tertiary care neonatal ICUs in Bangalore, India from October 1995 to May 1996
Interventions	Standard IVIG (Sandoglobin) 1g/kg for 3 consecutive days vs placebo using 0.15% saline in 10% dextrose in non-identical vials
Outcomes	Mortality at the end of the study period Duration of hospital stay
Notes	No adverse effect was reported in the IVIG or placebo infusions in any of the 3 centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number allocation was done at a co-ordinating centre
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes
Blinding (performance bias and detection bias) Mortality	High risk	Non-identical vials
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven neonates eligible to enter the trial but could not afford the subsidized cost of the IVIG were enrolled into a separate control group and one baby who received only one dose of IVIG was excluded from the analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Placebo group had a higher number of babies with positive cultures

Tugrul 2002

Methods	RCT
Participants	Patients with severe sepsis in Turkey Age range of patients 10 to 76 years old
Interventions	IgM-enriched IVIG at 5 ml/kg/day infused over 6 hrs and repeated for 3 consecutive days versus standard sepsis therapy
Outcomes	28-day mortality ICU length of stay
Notes	Based on communication of Pildal and Goetzsche (Pildal 2004); open table of random numbers at allocation site

Risk of bias

Bias	Authors' judgement	Support for judgement

Tugrul 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	High risk	Open table of random numbers at allocation site
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Weisman 1992

Methods	RCT, multi-centre
Participants	Premature neonates with early-onset sepsis confirmed by blood culture 9 institutions in USA from June 1985 - April 1989
Interventions	Standard IVIG (lyophilised Sandoglobulin) 500mg/kg single infusion for 2 hrs versus albumin (lyophilised) in identical vials
Outcomes	Mortality at 3 days, 7 days and 56 days post-infusion Duration of hospitalisation Serum IgG levels GBS type-specific serum IgG levels Adverse reactions
Notes	Six suspected infusion-related adverse reactions, four in the albumin group (hypotension) and two in the IVIG group (hypotension and hypoglycaemia); P=0.70

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drug vials were randomly selected in groups of 50 by institution, to contain either IVIG or albumin. Each enrolled patient received the next vial of drug available at the institution The pharmacy reconstituted the drug vials
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, identical vials
Incomplete outcome data (attrition bias)	Low risk	

Weisman 1992 *(Continued)*

All outcomes	
Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Werdan 2007

Methods	RCT
Participants	Patients with score-defined sepsis (sepsis score 12 to 27) and score-defined sepsis-induced severity of diseases (APACHE II score 20-35) in 23 surgical and medical ICUs in university centres and large teaching hospitals in Germany from January 1991 to April 1995
Interventions	IVIG (5% Polyglobin N) administered as 12 ml (600 mg/kg) on day 0 and 6 ml (300 mg/kg) on day1 versus placebo consisting of 0.1% human serum albumin, identical in appearance to the IVIG
Outcomes	28-day all-cause mortality; 7-day mortality; 4-day pulmonary function
Notes	19 adverse events reported in 17 patients: 6 adverse events in 6 patients in the placebo group - 3 skin reactions, 1 respiratory insufficiency, 1 hypotension, 1 septic shock; 13 adverse events in 11 patients in the IVIG group - 6 skin reactions (erythema, exanthem), 1 anaphylactic reaction, 1 congestion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Serial random numbers were used
Allocation concealment (selection bias)	Low risk	Identity of the medication that each patient received was marked on a card and a copy was forwarded as part of the confidential study documents to Troponwerke, Cologne
Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Wesoly 1990

Methods	RCT, single centre
Participants	Adults with post-operative sepsis

Wesoly 1990 *(Continued)*

	Department of Surgery in a university hospital in Germany during a 12-month period
Interventions	Standard IVIG (Pentaglobin)
Outcomes	All-cause mortality. Duration of hospitalisation
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Based on communication of Pildal and Goetzsche (Pildal 2004) - inadequate allocation concealment (alternation)
Blinding (performance bias and detection bias) Mortality	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Unclear risk	Control group had a higher mean age, fewer patients on antibiotics and fewer patients on artificial ventilation

Yakut 1998

Methods	Randomized, single centre - Turkey
Participants	Adult surgical patients with severe sepsis 1992-96
Interventions	IgG (Gamumine N) 0.4g/kg on days 0 and 1, 0.2 g/kg on days 2-4 versus human albumin
Outcomes	Mortality
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Not stated

Yakut 1998 *(Continued)*

Blinding (performance bias and detection bias) Mortality	Low risk	Placebo-controlled, identical bottles
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	Low risk	

Ziegler 1991

Methods	RCT, multi-centre, multi-national
Participants	Adult patients,18 years or older, with gram-negative bacteraemia 24 academic medical centres in USA, Canada and Europe
Interventions	HA-1A 100 mg single infusion for 15 -20 min versus 3.5 g human serum albumin
Outcomes	28-day all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Independent co-ordinating centre created the treatment allocation code
Blinding (performance bias and detection bias) Mortality	Low risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 37% analysed from 543 patients given HA-1A for the primary outcome reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Baseline characteristics not given for the 543 patients initially randomized

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aitchison 1985	The human anti-lipopolysaccharide specific globulin (LG-1) was administered intramuscularly and not by the intravenous route
Bojic 1998	This was not a randomized controlled trial
Cairo 1992	Granulocyte transfusion was the intervention while IVIG was the drug in the control group
Calandra 1988	The comparator group was IVIG
Christensen 1991	This was a pilot study where the primary outcome measure was not mortality but on the effect of IVIG on neutrophil kinetics and serum opsonic capacity. The survival of neonates in both the experimental and control groups was 100%
De Groote 1989	The primary outcome measure was not mortality; TNF levels were the main variables of interest in the study
Dominioni 1991	This is an interim analysis. We have included the full analysis of this trial (Dominioni 1996)
El Nawawy 2005	Alternate allocation of treatment was used based on communication with the author
Fischer 1983	An animal model was used
Fisher 1993	This was mainly a dose-ranging study with no control group
Fisher 1996	Tumour necrosis factor:Fc fusion protein is not a monoclonal antibody
Freeman 1999	This was a meta-analysis of clinical trials of anti -inflammatory agents for sepsis rather than an RCT
Gokalp 1994	Alternate allocation was used and the study included patients with specific infection - Salmonella typhi, not necessarily sepsis
Gunes 2006	This was a quasi-randomized trial. Infants were enrolled consecutively at the first episode of infection and divided into three groups by someone included in the study
Haque 1995	This was an RCT comparing standard IVIG to IgM-enriched IVIG. The two treatment groups were also compared to matched controls, but the latter were not part of the randomization scheme
Homan 1990	The primary outcome was not mortality
Jaspers 1987	This an interim analysis of 16 patients (9 anti-Lipid A, 6 placebo) with no indication in the 2008 search whether there was a full report
Jenson 1997	This was not an RCT but a meta-analysis on prevention and treatment of neonatal sepsis with IVIG
Jesdinsky 1987	This was an RCT on the use of IVIG in patients with specifically diffuse fibrinopurulent peritonitis and not necessarily sepsis
Jones 1995	IVIG was used for prophylaxis; outcome was not mortality
Kaul 1999	This was not an RCT but an observational study
Kay 1996	Open-label phase 2 trial on an anti-TNF (MAK-195F Knoll); unable to retrieve this unpublished trial presented in a conference
Kett 1994	Outcome measures were not morbidity nor mortality

Study	Reason for exclusion
Kornelisse 1997	A subset of 49 children in this study were included in the large multi-centre RCT of HA-1A human mAb (Derkx 1999) which has been reviewed in this meta-analysis
Kreymann 2007	This is a meta-analysis of polyclonal IVIG
Lacy 1995	This was not an RCT but a meta-analysis of prophylaxis or treatment with IVIG
Laupland 2007	This is a meta-analysis of polyclonal IVIG
Marenovic 1998	Alternate allocation of treatment
Okimoto 1985	There was no control group
Panko 1976	This was not an RCT
Pilz 1997	This was an RCT comparing IgM-enriched immunoglobulin to polyvalent IgG as the control group
Pittet 1999	Tumour necrosis factor:Fc fusion protein is not a monoclonal antibody
Schedel 1996	The RCT in this paper written in Russian was originally reported in Schedel 1991
Sidiropolous 1981	Alternate allocation of treatment
Sidiropoulos 1986	Alternate allocation of treatment
Tomii 1985	This was not an RCT; there was no control group
Turgeon 2007	This is a meta-analysis of polyclonal IVIG
Ueda 1985	There was no control group
Wang 2006	Outcome is not mortality
Werdan 1996	This was a critical appraisal and not a randomized controlled trial
Wortel 1992	This was a substudy of a large multi-centre trial on HA-1A by Ziegler 1991, which has been included in this meta-analysis. It focused mainly on the effect of HA-1A on mortality and cytokine levels of septic patients with endotoxaemia
Yavuz 2012	This was not a randomized controlled trial but rather a retrospective study
Zeni 1997	This was not a randomized controlled trial but rather an editorial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Yildizdas 2005

Methods	Prospective randomized
Participants	84 children with sepsis in the paediatric intensive care unit , mean age 32.6, SD 32.1 months, 60 had blood culture proven sepsis
Interventions	IVIG 1g/kg/d for 2 days

Yildizdas 2005 *(Continued)*

Outcomes	Mortality
Notes	Duration of hospitalisation (10.8, SD 3.2 days versus 11, SD 3 days) Mortality rate (8/30 versus 10/30) Unable to retrieve full text. Unable to determine from the abstract whether randomization and allocation concealment is adequate

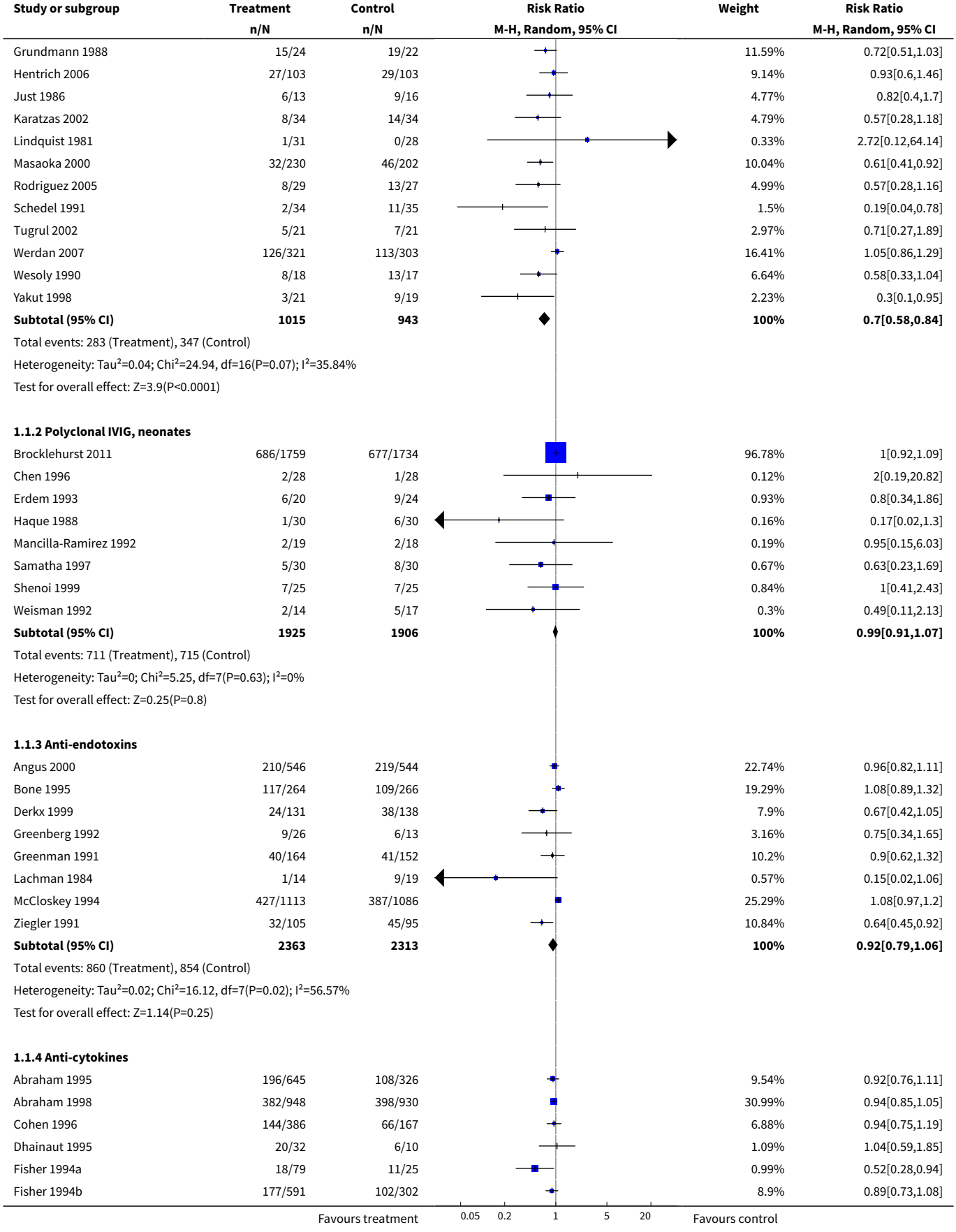
DATA AND ANALYSES

Comparison 1. IVIG versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality by type of IVIG, random effects	42		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Polyclonal IVIG, adults	17	1958	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.2 Polyclonal IVIG, neonates	8	3831	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
1.3 Anti-endotoxins	8	4676	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.06]
1.4 Anti-cytokines	9	7893	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.97]
2 Low risk of bias studies, all-cause mortality	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Polyclonal IVIG, adults	5	945	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.18]
2.2 Polyclonal IVIG, neonates	3	3561	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.92, 1.08]
2.3 Anti-endotoxins	1	269	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.42, 1.05]
2.4 Anti-cytokines	3	5065	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.99]

Analysis 1.1. Comparison 1 IVIG versus placebo or no intervention, Outcome 1 All-cause mortality by type of IVIG, random effects.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Polyclonal IVIG, adults					
Behre 1995	9/30	10/22		4.94%	0.66[0.32,1.35]
Burns 1991	4/25	3/13		1.69%	0.69[0.18,2.64]
Darenberg 2003	1/10	4/11		0.78%	0.28[0.04,2.07]
De Simone 1988	7/12	9/12		6.66%	0.78[0.44,1.39]
Dominioni 1996	21/59	38/58		10.52%	0.54[0.37,0.8]
	Favours treatment		0.05 0.2 1 5 20	Favours control	



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Opal 1997	116/350	126/346		8.6%	0.91[0.74,1.12]
Panacek 2004	421/1305	477/1329		31.48%	0.9[0.81,1]
Reinhart 1996	44/93	12/29		1.53%	1.14[0.71,1.85]
Subtotal (95% CI)	**4429**	**3464**		**100%**	**0.92[0.86,0.97]**
Total events: 1518 (Treatment), 1306 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.02, df=8(P=0.76); I^2=0%					
Test for overall effect: Z=2.86(P=0)					

Favours treatment 0.05 0.2 1 5 20 Favours control

Analysis 1.2. Comparison 1 IVIG versus placebo or no intervention, Outcome 2 Low risk of bias studies, all-cause mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Polyclonal IVIG, adults					
Burns 1991	4/25	3/13		2.9%	0.69[0.18,2.64]
Darenberg 2003	1/10	4/11		1.29%	0.28[0.04,2.07]
Hentrich 2006	27/103	29/103		21.87%	0.93[0.6,1.46]
Rodriguez 2005	8/29	13/27		9.78%	0.57[0.28,1.16]
Werdan 2007	126/321	113/303		64.16%	1.05[0.86,1.29]
Subtotal (95% CI)	**488**	**457**		**100%**	**0.94[0.74,1.18]**
Total events: 166 (Treatment), 162 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=4.55, df=4(P=0.34); I^2=12.16%					
Test for overall effect: Z=0.55(P=0.58)					
1.2.2 Polyclonal IVIG, neonates					
Brocklehurst 2011	686/1759	677/1734		99.49%	1[0.92,1.09]
Mancilla-Ramirez 1992	2/19	2/18		0.2%	0.95[0.15,6.03]
Weisman 1992	2/14	5/17		0.31%	0.49[0.11,2.13]
Subtotal (95% CI)	**1792**	**1769**		**100%**	**1[0.92,1.08]**
Total events: 690 (Treatment), 684 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.08(P=0.93)					
1.2.3 Anti-endotoxins					
Derkx 1999	24/131	38/138		100%	0.67[0.42,1.05]
Subtotal (95% CI)	**131**	**138**		**100%**	**0.67[0.42,1.05]**
Total events: 24 (Treatment), 38 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.77(P=0.08)					
1.2.4 Anti-cytokines					
Abraham 1998	382/948	398/930		44.68%	0.94[0.85,1.05]
Cohen 1996	144/386	66/167		9.92%	0.94[0.75,1.19]
Panacek 2004	421/1305	477/1329		45.4%	0.9[0.81,1]
Subtotal (95% CI)	**2639**	**2426**		**100%**	**0.92[0.86,0.99]**
Total events: 947 (Treatment), 941 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=2.21(P=0.03)					

Favours experimental 0.01 0.1 1 10 100 Favours control

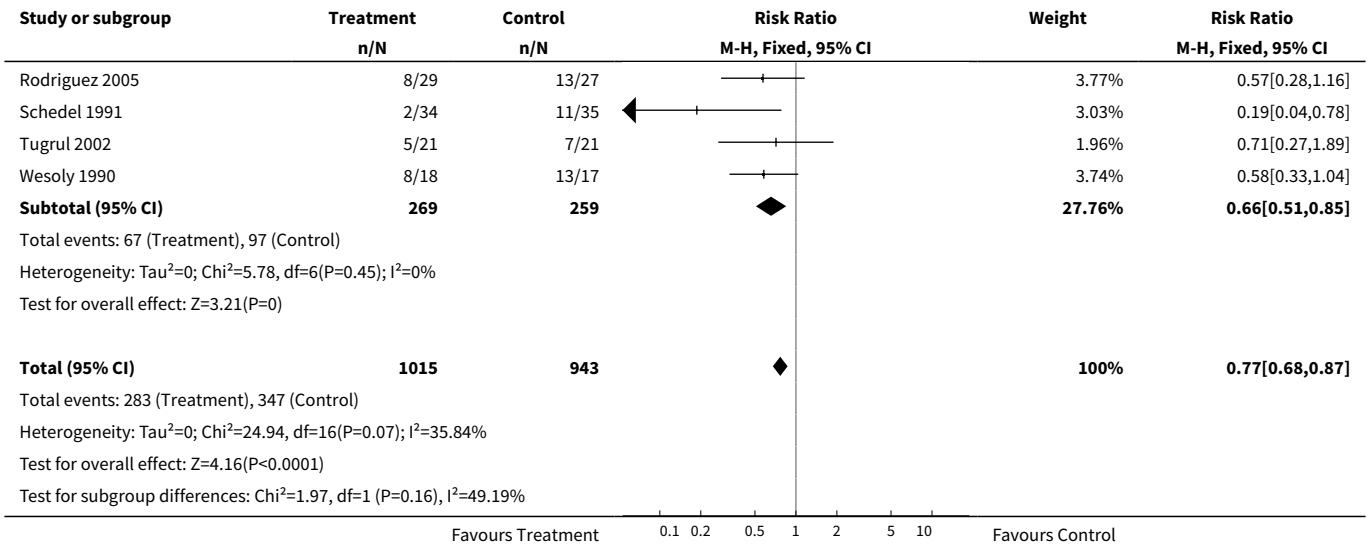
Comparison 2. Polyclonal IVIG versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality, adults, by type of polyclonal IVIG	17	1958	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
1.1 Standard polyclonal IVIG, adults	10	1430	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.93]
1.2 IgM-enriched polyclonal IVIG, adults	7	528	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.51, 0.85]
2 Sensitivity analysis, low risk of bias adult studies, by type of polyclonal IVIG, mortality all-cause	5	945	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.15]
2.1 Standard IVIG, adults, low risk of bias	3	683	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.24]
2.2 IgM-enriched IVIG, adults, low risk of bias	2	262	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.56, 1.19]
3 All-cause mortality, neonates, by type of polyclonal IVIG	8	3831	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.07]
3.1 Standard polyclonal IVIG, neonates	5	3667	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
3.2 IgM-enriched polyclonal IVIG, neonates	3	164	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.04]
4 Sensitivity analysis, low risk of bias, standard polyclonal IVIG, neonates, mortality all-cause	3	3561	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
5 Mortality from sepsis / septic shock	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Polyclonal IVIG, adult	4	414	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.29, 0.69]
5.2 Polyclonal IVIG, neonate	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.34, 1.86]
6 Length of hospital stay, survivors	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Polyclonal IVIG, adult	6	252	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-6.37, 0.38]
6.2 Polyclonal IVIG, neonate	5	198	Mean Difference (IV, Fixed, 95% CI)	-5.84 [-9.72, -1.95]
7 Sensitivity analysis by quality, length of hospital stay, neonates	3	111	Mean Difference (IV, Fixed, 95% CI)	1.39 [-12.18, 14.96]

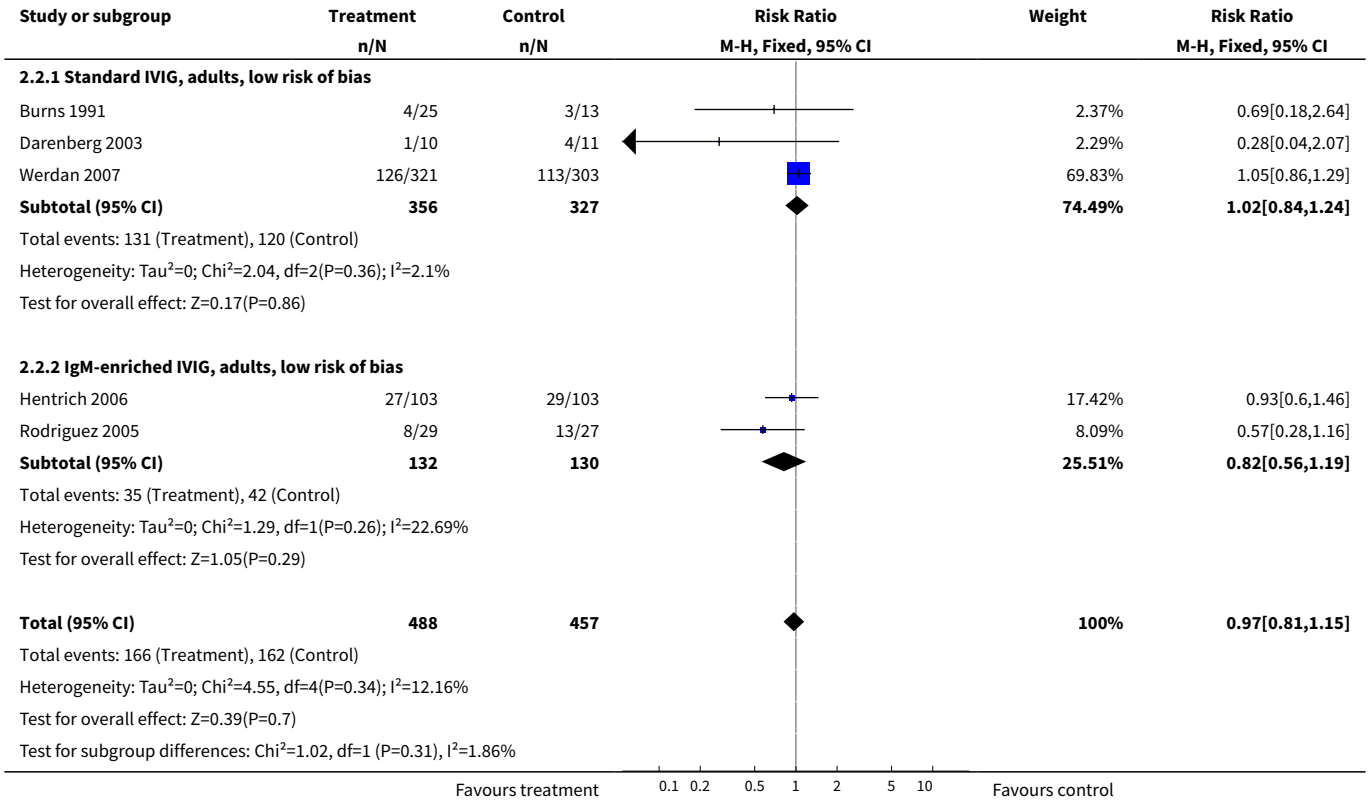
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 All-cause mortality, adults, by type of patients	17	1958	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
8.1 Surgical patients	5	294	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.45, 0.72]
8.2 Medical patients	9	987	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.51, 0.83]
8.3 Mixed medical-surgical	3	677	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.85, 1.23]
9 Sensitivity analysis, high quality trials, all-cause mortality polyclonal IVIG	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Standard IVIG, adults	3	683	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.24]
9.2 IgM enriched IVIG, adults	2	262	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.56, 1.19]
9.3 Standard IVIG, neonates	3	3561	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]

Analysis 2.1. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 1 All-cause mortality, adults, by type of polyclonal IVIG.

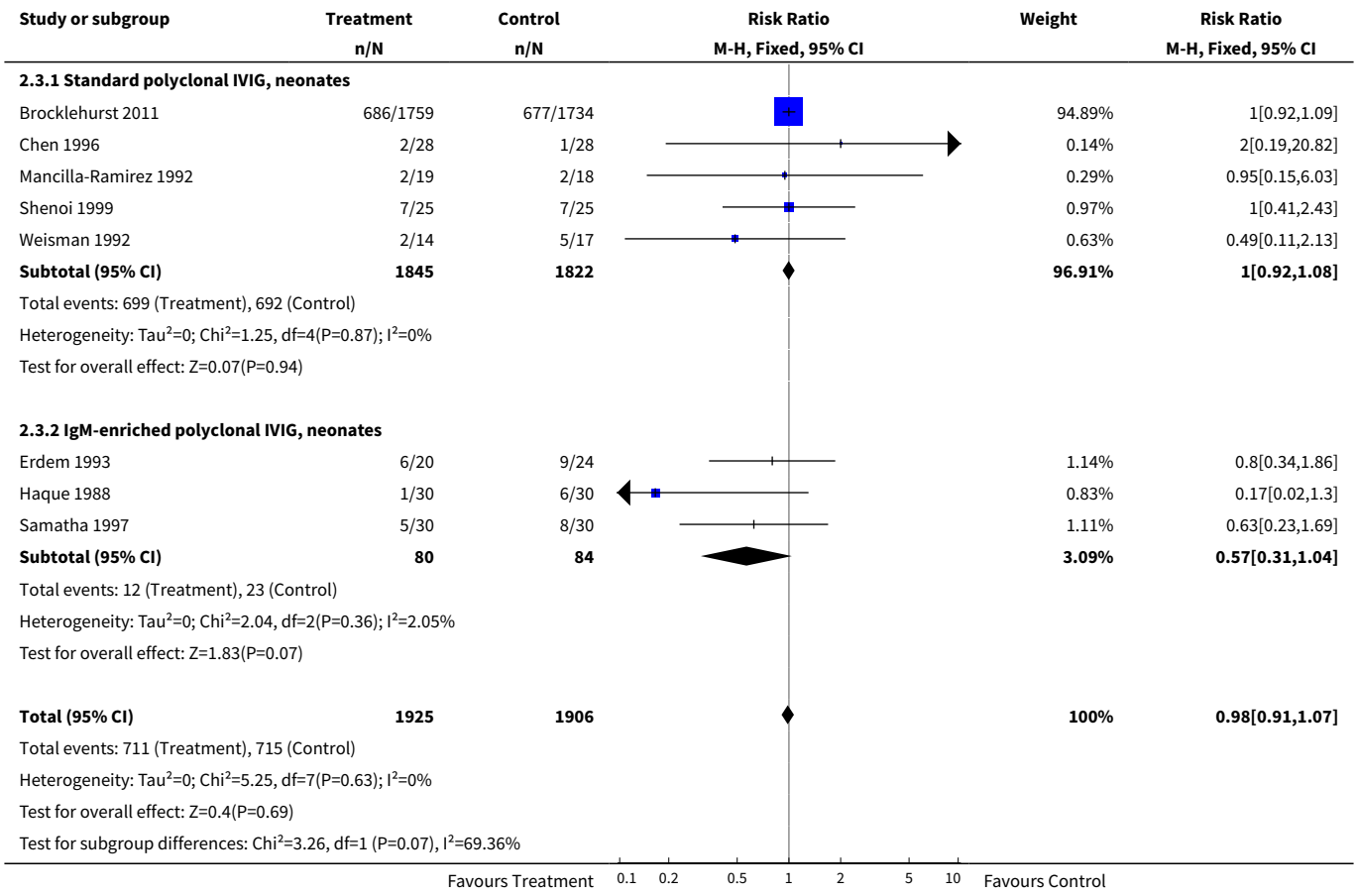
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Standard polyclonal IVIG, adults					
Burns 1991	4/25	3/13		1.1%	0.69[0.18,2.64]
Darenberg 2003	1/10	4/11		1.07%	0.28[0.04,2.07]
De Simone 1988	7/12	9/12		2.52%	0.78[0.44,1.39]
Dominioni 1996	21/59	38/58		10.72%	0.54[0.37,0.8]
Grundmann 1988	15/24	19/22		5.55%	0.72[0.51,1.03]
Just 1986	6/13	9/16		2.26%	0.82[0.4,1.7]
Lindquist 1981	1/31	0/28		0.15%	2.72[0.12,64.14]
Masaoka 2000	32/230	46/202		13.7%	0.61[0.41,0.92]
Werdan 2007	126/321	113/303		32.53%	1.05[0.86,1.29]
Yakut 1998	3/21	9/19		2.64%	0.3[0.1,0.95]
Subtotal (95% CI)	**746**	**684**		**72.24%**	**0.81[0.7,0.93]**
Total events: 216 (Treatment), 250 (Control)					
Heterogeneity: Tau^2=0; Chi^2=17.42, df=9(P=0.04); I^2=48.33%					
Test for overall effect: Z=2.9(P=0)					
2.1.2 IgM-enriched polyclonal IVIG, adults					
Behre 1995	9/30	10/22		3.23%	0.66[0.32,1.35]
Hentrich 2006	27/103	29/103		8.11%	0.93[0.6,1.46]
Karatzas 2002	8/34	14/34		3.92%	0.57[0.28,1.18]
		Favours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	



Analysis 2.2. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 2 Sensitivity analysis, low risk of bias adult studies, by type of polyclonal IVIG, mortality all-cause.

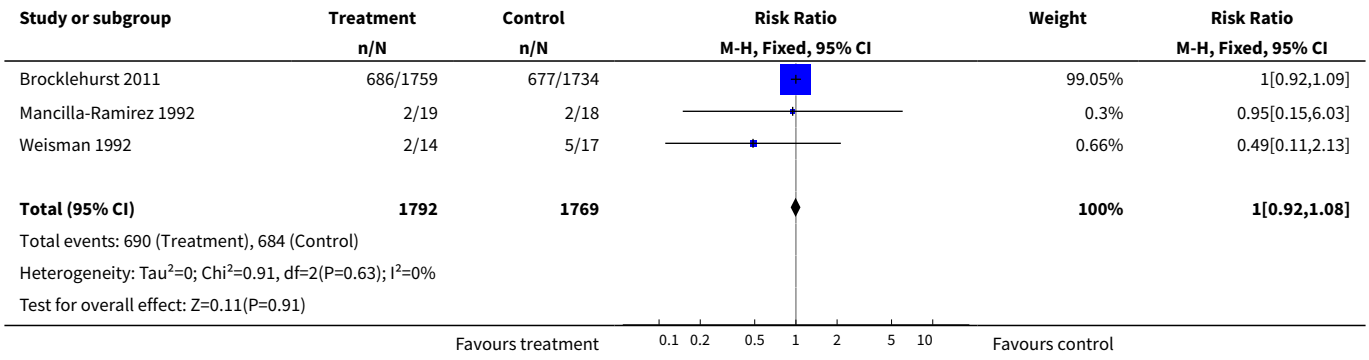


Analysis 2.3. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 3 All-cause mortality, neonates, by type of polyclonal IVIG.



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Standard polyclonal IVIG, neonates					
Brocklehurst 2011	686/1759	677/1734		94.89%	1[0.92,1.09]
Chen 1996	2/28	1/28		0.14%	2[0.19,20.82]
Mancilla-Ramirez 1992	2/19	2/18		0.29%	0.95[0.15,6.03]
Shenoi 1999	7/25	7/25		0.97%	1[0.41,2.43]
Weisman 1992	2/14	5/17		0.63%	0.49[0.11,2.13]
Subtotal (95% CI)	**1845**	**1822**		**96.91%**	**1[0.92,1.08]**
Total events: 699 (Treatment), 692 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.25, df=4(P=0.87); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					
2.3.2 IgM-enriched polyclonal IVIG, neonates					
Erdem 1993	6/20	9/24		1.14%	0.8[0.34,1.86]
Haque 1988	1/30	6/30		0.83%	0.17[0.02,1.3]
Samatha 1997	5/30	8/30		1.11%	0.63[0.23,1.69]
Subtotal (95% CI)	**80**	**84**		**3.09%**	**0.57[0.31,1.04]**
Total events: 12 (Treatment), 23 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.04, df=2(P=0.36); I^2=2.05%					
Test for overall effect: Z=1.83(P=0.07)					
Total (95% CI)	**1925**	**1906**		**100%**	**0.98[0.91,1.07]**
Total events: 711 (Treatment), 715 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.25, df=7(P=0.63); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Chi^2=3.26, df=1 (P=0.07), I^2=69.36%					

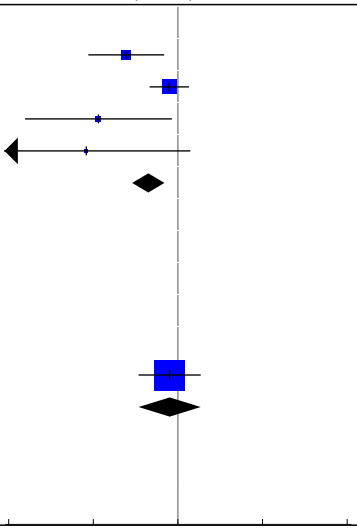
Analysis 2.4. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 4 Sensitivity analysis, low risk of bias, standard polyclonal IVIG, neonates, mortality all-cause.



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brocklehurst 2011	686/1759	677/1734		99.05%	1[0.92,1.09]
Mancilla-Ramirez 1992	2/19	2/18		0.3%	0.95[0.15,6.03]
Weisman 1992	2/14	5/17		0.66%	0.49[0.11,2.13]
Total (95% CI)	**1792**	**1769**		**100%**	**1[0.92,1.08]**
Total events: 690 (Treatment), 684 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					

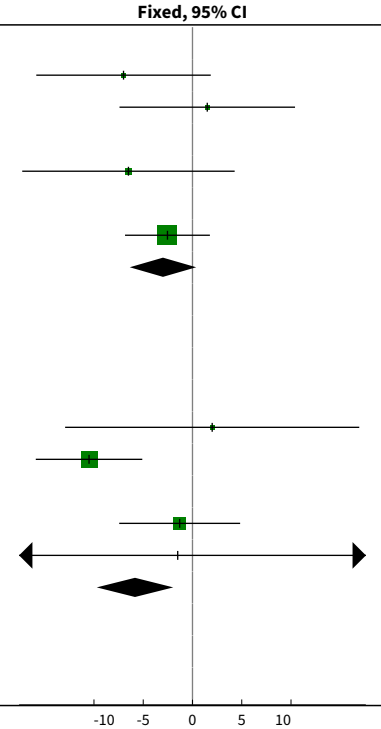
Analysis 2.5. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 5 Mortality from sepsis / septic shock.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Polyclonal IVIG, adult					
Dominioni 1996	4/57	16/56		29.49%	0.25[0.09,0.69]
Hentrich 2006	19/103	24/103		43.84%	0.79[0.46,1.35]
Schedel 1991	1/27	9/28		16.14%	0.12[0.02,0.85]
Yakut 1998	0/21	5/19		10.53%	0.08[0,1.4]
Subtotal (95% CI)	**208**	**206**		**100%**	**0.45[0.29,0.69]**
Total events: 24 (Treatment), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.8, df=3(P=0.03); I^2=65.89%					
Test for overall effect: Z=3.6(P=0)					
2.5.2 Polyclonal IVIG, neonate					
Erdem 1993	6/20	9/24		100%	0.8[0.34,1.86]
Subtotal (95% CI)	**20**	**24**		**100%**	**0.8[0.34,1.86]**
Total events: 6 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					



Analysis 2.6. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 6 Length of hospital stay, survivors.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.6.1 Polyclonal IVIG, adult							
Dominioni 1996	38	19 (17)	20	26 (16)		14.52%	-7[-15.85,1.85]
Grundmann 1988	24	22.8 (16.7)	22	21.3 (14.1)		14.34%	1.5[-7.41,10.41]
Just 1986	13	21 (0)	16	16.9 (0)			Not estimable
Lindquist 1981	22	20.9 (14.1)	20	27.4 (20.6)		9.79%	-6.5[-17.28,4.28]
Tugrul 2002	21	29 (0)	21	22 (0)			Not estimable
Wesoly 1990	18	13.3 (5.8)	17	15.8 (7.1)		61.36%	-2.54[-6.85,1.77]
Subtotal ***	**136**		**116**			**100%**	**-3[-6.37,0.38]**
Heterogeneity: Tau^2=0; Chi^2=2.21, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=1.74(P=0.08)							
2.6.2 Polyclonal IVIG, neonate							
Chen 1996	10	48 (16)	10	46 (18)		6.78%	2[-12.93,16.93]
Mancilla-Ramirez 1992	19	13.9 (5.7)	18	24.4 (10.3)		51.69%	-10.5[-15.9,-5.1]
Samatha 1997	30	20 (0)	30	29 (0)			Not estimable
Shenoi 1999	25	17 (10.4)	25	18.3 (11.7)		40.1%	-1.3[-7.44,4.84]
Weisman 1992	14	60.6 (34)	17	62.1 (57.3)		1.43%	-1.5[-34.04,31.04]
Subtotal ***	**98**		**100**			**100%**	**-5.84[-9.72,-1.95]**
Heterogeneity: Tau^2=0; Chi^2=6.09, df=3(P=0.11); I^2=50.71%							
Test for overall effect: Z=2.94(P=0)							
Test for subgroup differences: Chi^2=1.17, df=1 (P=0.28), I^2=14.5%							

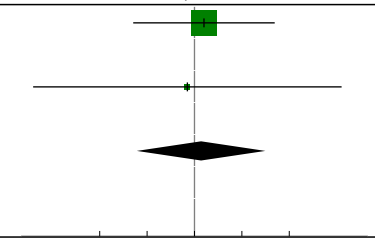


Analysis 2.7. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 7 Sensitivity analysis by quality, length of hospital stay, neonates.

Study or subgroup	Favours Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Chen 1996	10	48 (16)	10	46 (18)		82.62%	2[-12.93,16.93]
Samatha 1997	30	20 (0)	30	29 (0)			Not estimable
Weisman 1992	14	60.6 (34)	17	62.1 (57.3)		17.38%	-1.5[-34.04,31.04]
Total ***	**54**		**57**			**100%**	**1.39[-12.18,14.96]**

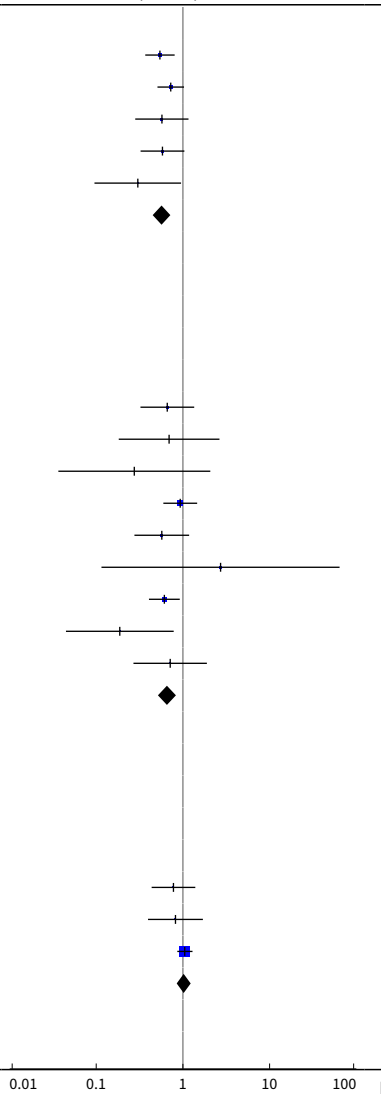
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.85); I²=0%

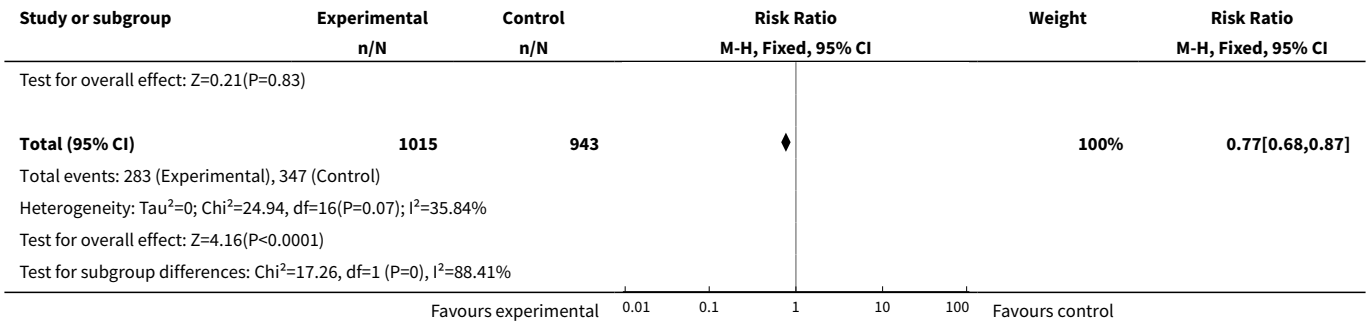
Test for overall effect: Z=0.2(P=0.84)



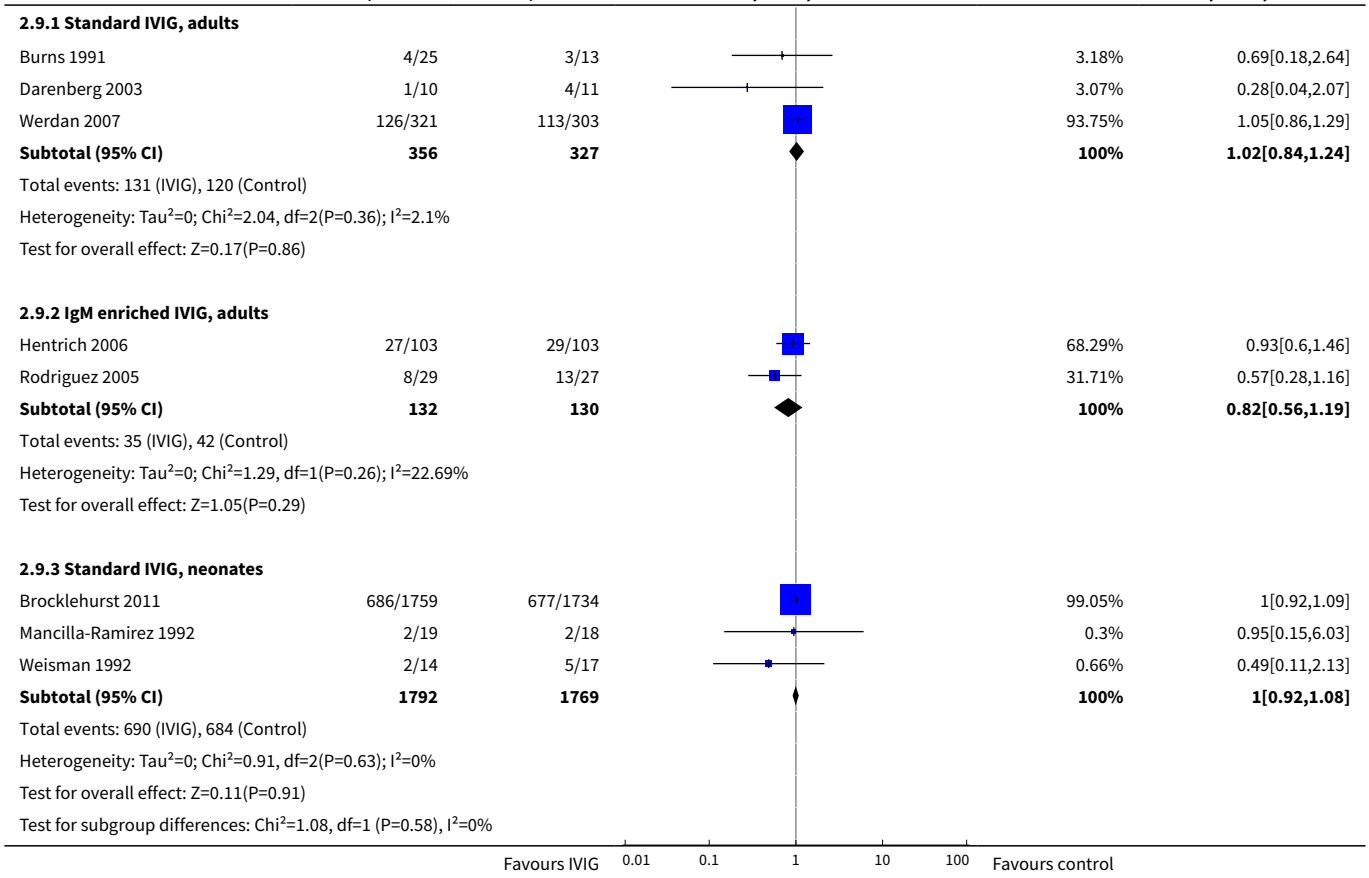
Analysis 2.8. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 8 All-cause mortality, adults, by type of patients.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Surgical patients					
Dominioni 1996	21/59	38/58		10.72%	0.54[0.37,0.8]
Grundmann 1988	15/24	19/22		5.55%	0.72[0.51,1.03]
Rodriguez 2005	8/29	13/27		3.77%	0.57[0.28,1.16]
Wesoly 1990	8/18	13/17		3.74%	0.58[0.33,1.04]
Yakut 1998	3/21	9/19		2.64%	0.3[0.1,0.95]
Subtotal (95% CI)	**151**	**143**		**26.42%**	**0.57[0.45,0.72]**
Total events: 55 (Experimental), 92 (Control)					
Heterogeneity: Tau²=0; Chi²=3.07, df=4(P=0.55); I²=0%					
Test for overall effect: Z=4.73(P<0.0001)					
2.8.2 Medical patients					
Behre 1995	9/30	10/22		3.23%	0.66[0.32,1.35]
Burns 1991	4/25	3/13		1.1%	0.69[0.18,2.64]
Darenberg 2003	1/10	4/11		1.07%	0.28[0.04,2.07]
Hentrich 2006	27/103	29/103		8.11%	0.93[0.6,1.46]
Karatzas 2002	8/34	14/34		3.92%	0.57[0.28,1.18]
Lindquist 1981	1/31	0/28		0.15%	2.72[0.12,64.14]
Masaoka 2000	32/230	46/202		13.7%	0.61[0.41,0.92]
Schedel 1991	2/34	11/35		3.03%	0.19[0.04,0.78]
Tugrul 2002	5/21	7/21		1.96%	0.71[0.27,1.89]
Subtotal (95% CI)	**518**	**469**		**36.27%**	**0.65[0.51,0.83]**
Total events: 89 (Experimental), 124 (Control)					
Heterogeneity: Tau²=0; Chi²=7.1, df=8(P=0.53); I²=0%					
Test for overall effect: Z=3.48(P=0)					
2.8.3 Mixed medical-surgical					
De Simone 1988	7/12	9/12		2.52%	0.78[0.44,1.39]
Just 1986	6/13	9/16		2.26%	0.82[0.4,1.7]
Werdan 2007	126/321	113/303		32.53%	1.05[0.86,1.29]
Subtotal (95% CI)	**346**	**331**		**37.3%**	**1.02[0.85,1.23]**
Total events: 139 (Experimental), 131 (Control)					
Heterogeneity: Tau²=0; Chi²=1.28, df=2(P=0.53); I²=0%					





Analysis 2.9. Comparison 2 Polyclonal IVIG versus placebo or no intervention, Outcome 9 Sensitivity analysis, high quality trials, all-cause mortality polyclonal IVIG.

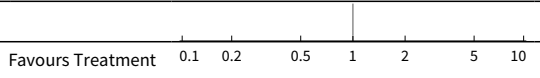


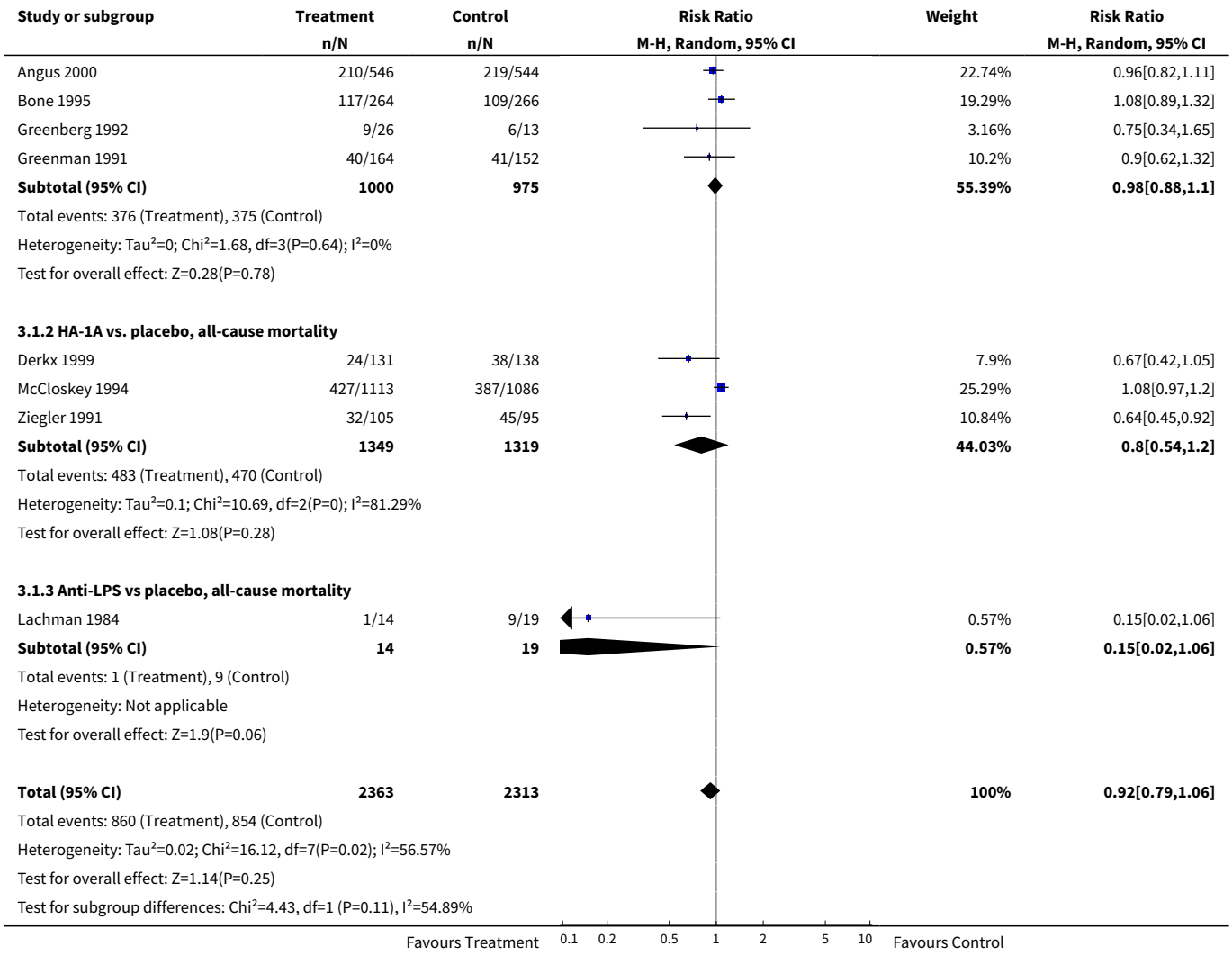
Comparison 3. Monoclonal antibodies versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anti-endotoxins vs. placebo, all-cause mortality	8	4676	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.06]
1.1 E5 vs. placebo, all- cause mortality	4	1975	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
1.2 HA-1A vs. placebo, all-cause mortality	3	2668	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.54, 1.20]
1.3 Anti-LPS vs placebo, all-cause mortality	1	33	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.06]
2 Sensitivity analysis by quality, anti-endotoxin, all-cause mortality	6	4443	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
2.1 Low risk of bias	1	269	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.05]
2.2 Unclear risk of bias	5	4174	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]
3 Anti-cytokines vs. placebo, all-cause mortality	9	7893	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.97]
3.1 Anti-TNF-alpha vs. placebo, all-cause mortality	6	6200	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.87, 0.99]
3.2 Human interleukin-1receptor antagonist vs. placebo, all-cause mortality	3	1693	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.76, 1.01]
4 Sensitivity analysis by quality, anti-cytokine, all-cause mortality	7	7752	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.97]
4.1 Low risk of bias	3	5065	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.99]
4.2 Uncertain risk of bias	4	2687	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 1.00]
5 Monoclonal antibody to Enterobacteriaceae common antigen	1	826	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.31]

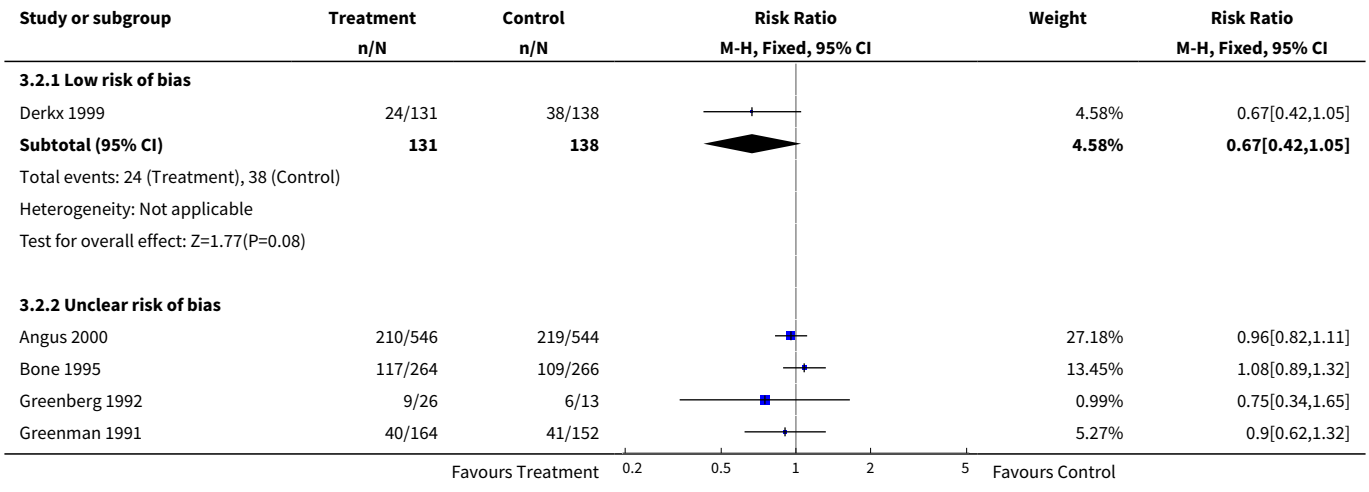
Analysis 3.1. Comparison 3 Monoclonal antibodies versus placebo, Outcome 1 Anti-endotoxins vs. placebo, all-cause mortality.

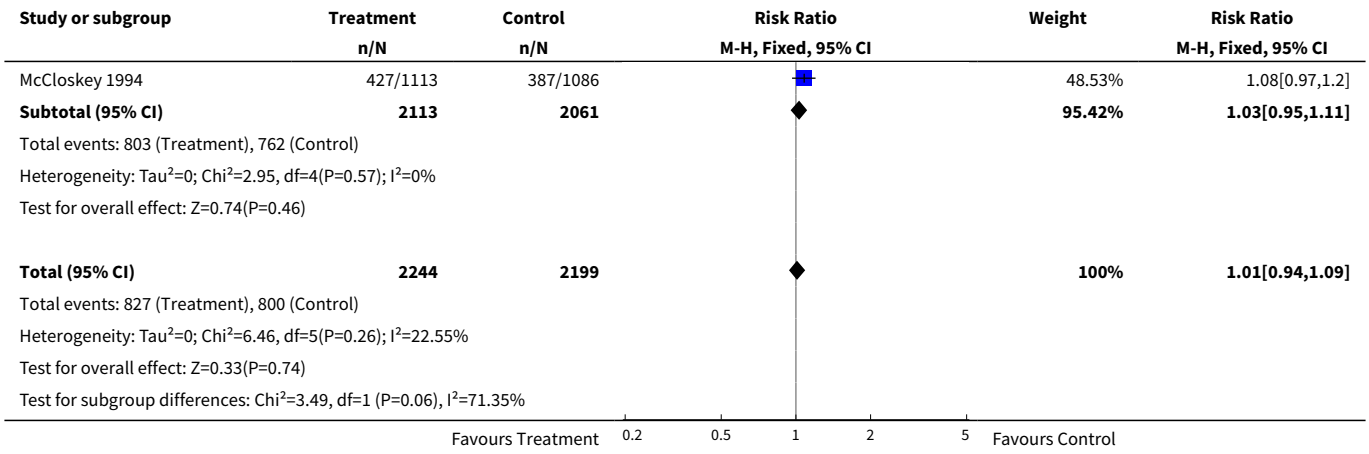
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 E5 vs. placebo, all- cause mortality					



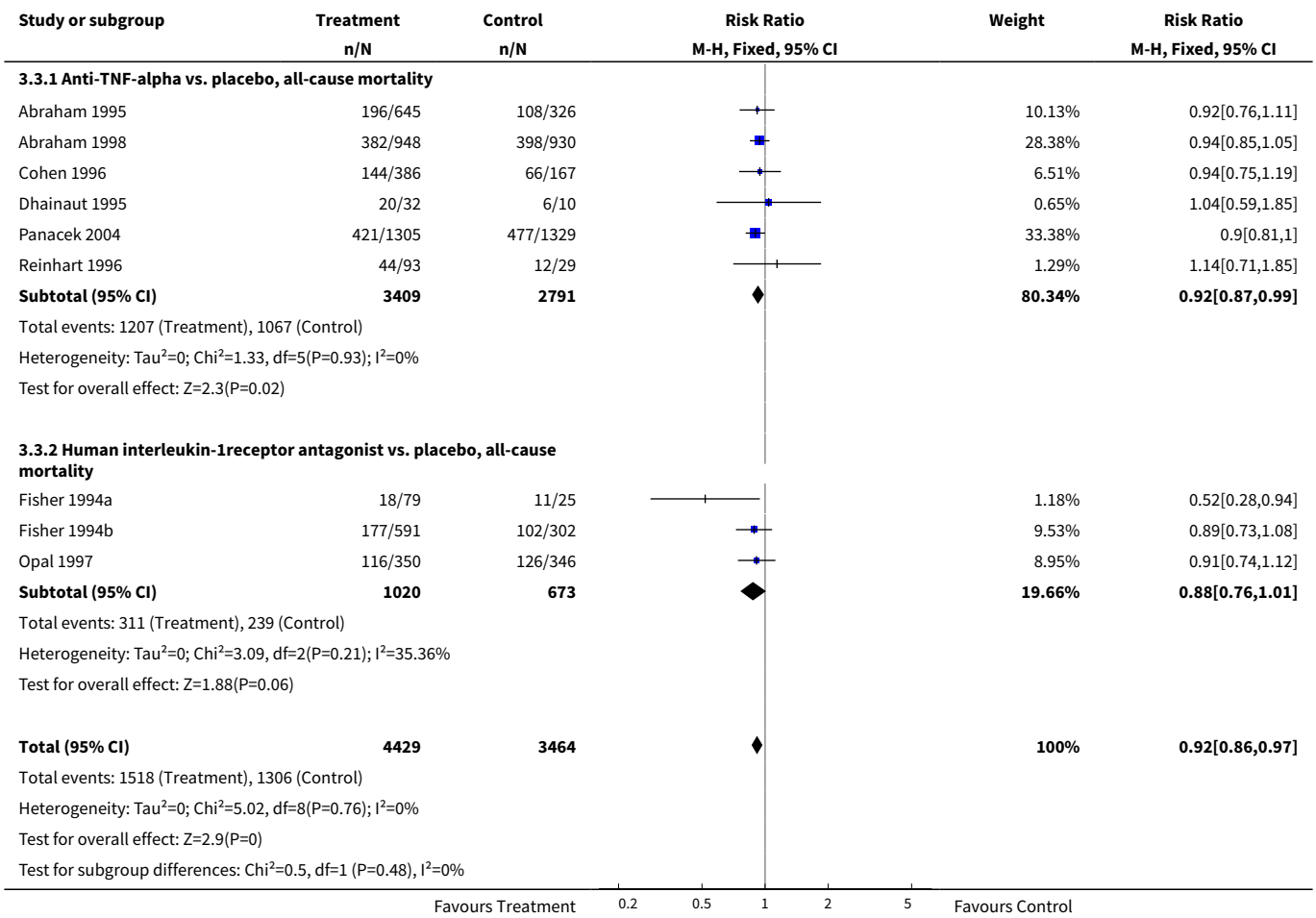


Analysis 3.2. Comparison 3 Monoclonal antibodies versus placebo, Outcome 2 Sensitivity analysis by quality, anti-endotoxin, all-cause mortality.



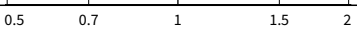


Analysis 3.3. Comparison 3 Monoclonal antibodies versus placebo, Outcome 3 Anti-cytokines vs. placebo, all-cause mortality.



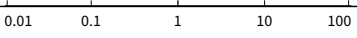
Analysis 3.4. Comparison 3 Monoclonal antibodies versus placebo, Outcome 4 Sensitivity analysis by quality, anti-cytokine, all-cause mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Low risk of bias					
Abraham 1998	382/948	398/930		28.89%	0.94[0.85,1.05]
Cohen 1996	144/386	66/167		6.63%	0.94[0.75,1.19]
Panacek 2004	421/1305	477/1329		33.99%	0.9[0.81,1]
Subtotal (95% CI)	**2639**	**2426**		**69.51%**	**0.92[0.86,0.99]**
Total events: 947 (Treatment), 941 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=2.25(P=0.02)					
3.4.2 Uncertain risk of bias					
Abraham 1995	202/664	109/330		10.47%	0.92[0.76,1.12]
Fisher 1994a	18/79	11/25		1.2%	0.52[0.28,0.94]
Fisher 1994b	177/591	102/302		9.71%	0.89[0.73,1.08]
Opal 1997	116/350	126/346		9.11%	0.91[0.74,1.12]
Subtotal (95% CI)	**1684**	**1003**		**30.49%**	**0.89[0.8,1]**
Total events: 513 (Treatment), 348 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.3, df=3(P=0.35); I^2=9.03%					
Test for overall effect: Z=2.01(P=0.04)					
Total (95% CI)	**4323**	**3429**		**100%**	**0.91[0.86,0.97]**
Total events: 1460 (Treatment), 1289 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4, df=6(P=0.68); I^2=0%					
Test for overall effect: Z=2.99(P=0)					
Test for subgroup differences: Chi^2=0.24, df=1 (P=0.63), I^2=0%					



Analysis 3.5. Comparison 3 Monoclonal antibodies versus placebo, Outcome 5 Monoclonal antibody to Enterobacteriaceae common antigen.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Albertson 2003	152/411	141/415		100%	1.09[0.91,1.31]
Total (95% CI)	**411**	**415**		**100%**	**1.09[0.91,1.31]**
Total events: 152 (Treatment), 141 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					



APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

#1 MeSH descriptor Immunoglobulins explode all trees
#2 MeSH descriptor Immunoglobulins, Intravenous explode all trees
#3 immunoglobulin* in All Text

#4 immunoglobulin* in All Text near/6 monoclon* in All Text)
#5 (immunoglobulin* in All Text near/6 polyclon* in All Text)
#6 IVIG in All Text
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 (sept* in All Text near/6 shock* in All Text)
#9 (septicem* in All Text or septicaem* in All Text or seps* in All Text)
#10 MeSH descriptor Sepsis explode all trees
#11 MeSH descriptor Septicemia explode all trees
#12 MeSH descriptor Shock, Septic explode all trees
#13 (#8 or #9 or #10 or #11 or #12)
#14 (#7 and #13)

Appendix 2. Search strategy for MEDLINE (OvidSP)

#1 exp Immunoglobulins/
#2 exp Immunoglobulin - Intravenous/
3 immunoglobulin$.mp.
#4 (immunoglobulin$ adj6 (monoclon$ or polyclon$)).mp.
#5 IVIG.mp.
#6 1 or 2 or 3 or 4 or 5
#7 ((sept$ adj6 shock$) or septicem$ or septicaem$ or seps$).mp.
#8 exp Sepsis/
#9 exp Septicemia/
#10 exp Shock-Septic/
#11 7 or 8 or 9 or#10
#12 6 and 11
#13 (randomized controlled trial.pt. or controlled clinical trial.pt.or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh.
#14 12 and 13

Appendix 3. Search strategy for EMBASE (OvidSP)

#1 immunoglobulin/
#2 immunoglobulin$.mp.
#3 ivig.mp.
#4 1 or 2 or 3
#5 sepsis/
#6 sepsis.mp.
#7 septic shock/
#8 (septic shock).mp.
#9 septicemia/
#10 septicaemia.mp.
#11 septicemia.mp.
#12 5 or 6 or 7 or 8 or 9 or 10 or 11
#13 4 and 12
#14 ((RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/) or ((RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab) and human*.ec,hw,fs.
#15 13 and 14

F E E D B A C K

Inclusion and omission of trials

Summary

The following points were raised about this review in a commentary by Doctors Cui and Eichacker (1999) published in the ACP Journal Club, 1999; 129: 70.

1. Inclusion of two RCTs in the monoclonal IVIG group (which provided 20% of the 4800 patients in the meta-analysis) on interleukin-1-receptor antagonist, a recombinant protein that is different from IVIG (Fisher 1994a; Fisher 1994b).
2. Omission of two large RCTs of 392 patients that showed that polyclonal IVIG did not reduce mortality in surgical patients with severe infection (Just 1986; Jesdinsky 1987).

3. Omission of a large RCT of 653 patients, where the preliminary results showed that polyclonal IVIG did not reduce mortality in sepsis (Werdan 1997 (abstract a).
4. Failure to cite a meta-analysis of 20 studies assessing six mediator-specific anti-inflammatory agents in 8808 patients with sepsis (Freeman 1999). A reduction in mortality was shown in eight of these studies that assessed anti-TNF monoclonal antibodies in more than 4000 patients.

Reply

1. Interleukin-1-receptor antagonist is functionally an anti-cytokine. Technically, it is a soluble inhibitor of IL-1activity. We recognize the structural heterogeneity of these monoclonal IVIGs, which accounts for the subgroup analyses. Even with inclusion or non-inclusion of these two trials, the overall conclusion would not significantly change with regards to the lack of benefit of anti-cytokines. Subgroup analyses of anti-TNF alpha and interleukin-1-receptor antagonist trials both yielded no significant reduction in mortality.

2. The trial by Jesdinsky (1987) was excluded because it did not fulfil the pre-specified inclusion criteria of our meta-analysis, i.e. study participants should be patients with sepsis or septic shock (protocol issue 2, 1998). Specifically, the trial by Jesdinsky (1987) was on patients with diffuse fibrinopurulent peritonitis, not necessarily sepsis. The trial by Just (1986), was initially excluded because of similar reasons; i.e. its inclusion criteria was severe infections in intensive care units. On English translation of the trial, there was a subgroup of 29 patients with sepsis and septic shock. This trial has now been moved into the included list and we have incorporated the outcome of this subgroup of sepsis patients in the updated version of the meta-analysis. The demonstrable benefit from polyclonal IVIG was maintained with the addition of this subgroup of patients.

3. The complete results of this large polyclonal RCT was supposed to be available by end of 1996 as stated in Werdan's (1996) review article. However, we were unable to retrieve this RCT in our most recent MEDLINE search (January 2000).

4. This meta-analysis included randomized and non-randomized trials and there was no mention whether a test for heterogeneity was done among the 20 studies on six different anti-inflammatory agents. Among the eight studies on anti-TNF that were included in this meta-analysis, five were included in the June 29, 1999 (Issue 4) updated version of our meta-analysis (Abraham 1995; Abraham 1998; Cohen 1996; Dhainaut 1995; Reinhart 1996). One trial (Fisher 1993) was excluded because there was no control group and was mainly a dose-ranging study. We do not have access yet to the full articles of the two other studies (Kay n.d.; Zeni 1997). The article by Zeni et al (1997) is indexed as a review article, not an RCT in the MEDLINE database, while the other article (Kay n.d.) is a presentation handout in a conference proceeding and is also not indexed in MEDLINE. It is also important to note that the largest (n = 1878) and most recent trial on anti-TNF alpha (Abraham 1998) did not show benefit in both the overall mortality analysis and various subgroups studied.

Contributors

Cui X, Eichacker PQ. National Institutes of Health, Bethesda, Maryland, USA (1999) published in the ACP Journal Club 1999; 129: 70.

Quality of the studies

Summary

The following issues were raised about this review in a commentary by Dr Peter C Gotzsche of the Nordic Cochrane Centre, received November 2001.

1. No description on how the reviewers assessed whether a trial had adequate concealment. This information is important, as trials with inadequate allocation concealment exaggerate the estimated effect by 30 to 40% on the average.
2. The expression good quality trials was used and analyses done accordingly, but it was not defined in the review in relation to the term high quality trials.
3. Exclusion of a trial written in Russian, which should be translated and included, as language bias has been demonstrated to exist.
4. Results section does not take the authors' quality assessment into account. There appears to be only two high quality trials with small sample sizes but a significant reduction in all-cause mortality using polyclonal IVIG was reported in the abstract and results section. Thus the result is somewhat doubtful, as it could have been influenced by publication bias and other biases related to small samples.
5. An effect on adults is reported but not on neonates. However, relative risk for adults and neonates are the same (RR = 0.60). It is therefore not reasonable to distinguish between the two situations, e.g. a test for interaction would not have yielded a significant result.
6. Lack of caution in the reporting of results in the abstract, i.e. the problem of small sample sizes was mentioned in the discussion but not in the abstract.
8. References could not be checked because the journal citation is missing, specifically for Haque 1988 and Lachman 1984.
7. Discrepancy in the classification of the trial of Schedel 1991 as having unclear allocation concealment in the main text, but with adequate allocation concealment in the table of included studies. It is suggested that the randomization be explained carefully in the table of included studies, as this information is essential for judging the quality of studies and for judging the robustness of the review's findings.

Reply

1. Trials were assessed by the reviewers to have adequate allocation concealment if randomization was administered by an independent third party through a central facility or the use of sealed opaque envelopes. This statement has been added in the methods section.

2. We recognize that the term good quality was not defined explicitly. The term good quality in the sensitivity analyses actually referred to both high quality and fair quality trials. For consistency and clarity we have removed the term good quality and used the actual terms: high quality, fair quality and low quality. Fair quality referred to those trials which have any one or more of the following biases: unclear allocation concealment, absence of blinding and lack of intention-to-treat analysis. We have made the necessary corrections in the text, particularly in the methods section and in the graphs. Low quality trials are those which have any one of the following biases: significant differences in the baseline characteristics of the treatment and control groups which are known predictors of outcome; marked differences in the dropout rates and overt differences in the general quality of care received by both groups such as differential administration of co-interventions. These definitions have been added in the methods section.
3. The Russian study has been translated previously and found to have been published originally in Engish (Schedel 1991). The English version is already included in our analyses. For clarity, we have revised the statement pertaining to this in the section of excluded studies.
4. Sensitivity analysis of the two high quality trials on polyclonal IVIG has been incorporated. This likewise showed significant reduction of mortality, although the confidence interval was wide (RR 0.30; 95% CI 0.09, 0.99; n = 91). Further subanalysis according to allocation concealment also showed a significant reduction of mortality (RR 0.43; 95% CI 0.25, 0.75, n =170).
5. A subanalysis on the effect of IVIG according to age group, i.e. adults and neonates was done based on clinical grounds. Physiologically, adults and neonates inherently differ from each other. The point estimates of the relative risks for adults (RR = 0.62) and neonates (RR = 0.70) differ, although their 95% CIs overlap. Statistically there may be no significant interaction between the two groups, but clinically adult and neonatal sepsis differ pathophysiologically , which is the main reason for the subgroup analysis.
6. We have revised the conclusion in the abstract to caution the readers with regards to the small sample sizes of the trials. One of the main reasons, however, for doing a meta-analysis is to increase the power of trials with small sample sizes.
7. Thank you for pointing this out. We have put in the proper citation, which was missed out in the reference section of included studies. The trial by Lachman (Lachman 1984) was published in the Lancet, while the trial by Haque (Haque 1988) was published in the American Journal of Diseases in Childhood.
8. Again thank you for this. The inadvertent discrepancy has been corrected in the text. On review of our files and the original article, the trial by Schedel (Schedel 1991) was definitely assessed to have adequate allocation concealment.

Contributors

Gotzsche, Peter C. The Nordic Cochrane Centre. October 2001

Mortality data

Summary

The following issues were raised about this review by Dr Peter C Gotzsche and Dr Julie Pildal of the Nordic Cochrane Centre, received July 2006.

You reported an effect of polyclonal immunoglobulin on overall mortality (11 trials, 176 deaths, relative risk (RR) 0.64 (95% confidence interval (CI) 0.51 to 0.80) but also noted that the trials were small and that the evidence was insufficient to support a robust conclusion of benefit.

We have replicated this part of your review (1) and found 21 trials and three times as many deaths. One of the trials was large, was of high quality, and had a pre-published protocol. Until the publication of our review, its results had only been available in an abstract that stated that the mortality was not reduced (2), but we obtained mortality data from the author.

We found that the apparent effect of polyclonal immunoglobulin was conveyed by trials at higher risk of being biased. These trials (292 deaths) showed RR 0.61 (95% CI 0.50 to 0.73), whereas the high quality trials (255 deaths) showed RR 1.02 (95% CI 0.84 to 1.24). The difference between the estimates from the trials of high methodological quality versus those from the trials of lower methodological quality was highly statistically significant (P = 0.0002).

In July 2004, we sent you our paper (1) where all the additional mortality data are available and also the additional trial reports. We anticipated that you would update your review or quote our research if the update was delayed because of lack of time. As this has not yet happened, we wish with this comment to warn clinicians against using polyclonal immunoglobulin for bacterial sepsis as we believe there is no reliable evidence that it works, and as it is very expensive.

1. Pildal J, Gøtzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis 2004; 39(1):38-46.
2. Werdan K, Pilz Gat SSG. Polyvalent immune globulins [abstract 18]. Shock 1997; 7(Suppl):5.

Reply

Thank you for the cautionary note on the absence of reliable evidence on the use of polyclonal immunoglobulin for bacterial sepsis. We concur, as stated in the conclusion of our 2003 update, which provides the same recommendation that "the trials were small and the totality of evidence is insufficient to provide a robust conclusion of benefit".

We note that Pildal and Gotzsche's (2004) main arguments and conclusion primarily hinged on a large trial (N = 653) by Werdan et al (1997), which remains unpublished to date. Our 2003 update did mention that we were awaiting the publication of this trial. However, we wonder

why a large RCT such as this remains unpublished, despite the increasing awareness of editors on the importance of negative trials and the advent of open-access electronic journals. Unfortunately unlike Pildal and Gotzsche who were able to communicate directly with Werdan et al, we do not have access to the full text of Werdan's study and are unable to review this pivotal work. Nevertheless, we will do a sensitivity analysis with and without the unpublished trial of Werdan et al in the update that we are currently doing.

Since our 2003 update, we and the Cochrane Anesthesia Review Group Trial Search Coordinator have updated the search of MEDLINE, EMBASE and the Cochrane CENTRAL databases using additional free text and MeSH terms and the highly sensitive search strategy in the *Cochrane Handbook for Systematic Reviews of Interventions*. In addition to the studies in Pildal and Gotzsche's review (Behre 1995; Burns 1991; Darenberg 2003; Dominioni 1996; Karatzas 2002; Lindquist 1981; Mancilla-Ramirez 1992; Samatha 1997; Tugrul 2002; Werdan 1997; Yakut 1998), we have identified another five potentially relevant trials (El Nawawy 2005; Gunes 2006; Hentrich 2006; Rodriguez 2005; Yildizdas 2005). We have also obtained mortality data for the trial of Masaoka et al (2000). These will be included in the 2006 update.

Please watch out for the results of the upcoming update of our review.

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Pildal J, Gøtzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis 2004; 39:38-46.

Contributors

Dr Peter C Gotzsche and Dr Julie Pildal of the Nordic Cochrane Centre, received July 2006

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 1999

Date	Event	Description
12 September 2013	New search has been performed	We reran the search from October 2008 to December 2012.
12 September 2013	New citation required and conclusions have changed	1. We included one new completed polyclonal IVIG trial previously classified as ongoing (Brocklehurst 2011). 2. One small trial on polyclonal IVIG in children is awaiting translation and full assessment (Yildizdas 2005). 3. There is a substantial change in the conclusions of the review with the inclusion of the large polyclonal IVIG trial in neonates (Brocklehurst 2011). There is now sufficient evidence that standard polyclonal IVIG in neonates does not reduce mortality.
15 December 2008	New search has been performed	Search reran up to October 2008; 16 new studies included: 14 polyclonal (Behre 1995;Burns 1991;Darenberg 2003;Dominioni 1996;Hentrich 2006;Karatzas 2002;Lindquist 1981; Mancilla-Ramirez 1992; Masaoka 2000;Rodriguez 2005; Samatha 1997;Tugrul 2002;Werdan 2007;Yakut 1998) and 2 monoclonal (Albertson 2003;Panacek 2004).
4 June 2008	Amended	Converted to new review format.
1 June 2008	New citation required and minor changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

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Conceiving the review: MAL

Co-ordinating the review: MAL, MMA

Undertaking manual searches: MMA

Screening search results: MAL, MMA

Organizing retrieval of papers: MMA

Screening retrieved papers against inclusion criteria: MAL, MMA

Appraising quality of papers: LFD, JBM

Abstracting data from papers: LFD, JBM, MMA

Writing to authors of papers for additional information: MMA

Providing additional data about papers: not applicable

Obtaining and screening data on unpublished studies: not applicable

Data management for the review: MMA

Entering data into Review Manager (RevMan 5.2): MMA

RevMan statistical data: MMA

Other statistical analysis not using RevMan: not done

Double entry of data: not done

Interpretation of data: MMA, MAL, JBM, LFD

Statistical inferences:

Writing the review: MMA, MAL

Securing funding for the review:

Performing previous work that was the foundation of the present study:

Guarantor for the review (one author): MMA

Person responsible for reading and checking review before submission: MMA, MAL

DECLARATIONS OF INTEREST

Marissa M Alejandria: none known

Mary Ann D Lansang: none known

Leonila F Dans: travel grant from Novartis to attend a meeting of pediatric rheumatologists to discuss the management of systemic onset juvenile idiopathic arthritis in November 2012.

Jacinto Blas Mantaring III: Dr Mantaring is the chair of the National Institutes of Health Ethics review board and a member of the Technical review board, who receives an honorarium for reviewing studies and attending meetings. He is also asked by government agencies, WHO and pharmaceutical companies to give lectures, conduct workshops and prepare educational materials on a variety of topics mostly related to research methods, evidence-based medicine and ethics as well as topics on neonatal care.

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (for example through employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- University of the Philippines, Manila, Philippines.

External sources

- Department for International Development, UK.
- European Commission (Directorate General XII), Belgium.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has been modified to include the term 'severe sepsis'. We included adverse effects in the list of outcome measures. We did a post hoc subgroup analysis of the included trials for adults and neonates.

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Immunoglobulins, Intravenous [*therapeutic use]; Randomized Controlled Trials as Topic; Sepsis [*drug therapy] [mortality]; Shock, Septic [*drug therapy] [mortality]

MeSH check words

Adult; Humans; Infant, Newborn